Enantioselectivity of Nickel(II) and Copper(II) Complexes of Schiff Bases derived from Amino Acids and (*S*)-*o*-[(*N*-Benzylprolyl)amino]-acetophenone or (*S*)-*o*-[(*N*-Benzylprolyl)amino]benzaldehyde. Crystal and Molecular Structures of [Ni{(*S*)-bap-(*S*)-Val}] and [Cu{(*S*)-bap-(*S*)-Val}] †

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Copper(II) and nickel(II) complexes of Schiff bases derived from (*S*)-*o*-[(*N*-benzylprolyl)amino]-acetophenone [(*S*)-bap] and the amino acids (aa): glycine, (*R*)- and (*S*)-alanine, (*R*)- and (*S*)-valine (val), (*R*)- and (*S*)-adamant-1-ylalanine, and (*R*)- and (*S*)-adamant-1-ylglycine have been synthesized. The structure of the complexes has been determined by physical and chemical methods; in addition the structures of [Cu{(*S*)-bap-(*S*)-Val}] and [Ni{(*S*)-bap-(*S*)-Val}] have been determined by *X*-ray crystallographic analysis. The kinetic CH-acidity and deuterium exchange of the hydrogen of an amino acid moiety under the action of bases has been studied. The deuterium exchange is accompanied with epimerization which results in 80% excess of the (*S*)-2-[^{2}H]amino acid. The stereoselectivity in the nickel complexes has been found to be higher than in the copper ones. The epimerization rate constant lies within the range 5×10^{-4}—1.2×10^{-1} dm^3 mol^{-1} s^{-1}. The observed stereoselective effects are interpreted on the basis of *X*-ray analysis, circular dichroism, and ^{1}H n.m.r. spectroscopic data. It is suggested that the [Ni{(*S*)-bap-aa}] complexes can be used for determining the absolute configuration of the amino acids.

Enantioselective effects in complexes of transition metals constitute an interesting area of modern inorganic chemistry.[1] Asymmetric synthesis [2] and resolution of racemates [3] may be cited as examples of practical applications of these effects.

Chiral recognition of enantiomers or prochiral groups in the complexes occurs mainly due to the steric intramolecular interaction of one chiral ligand with another chiral ligand or with prochiral groups of a neighbouring ligand. The difficulty in selecting an appropriate chiral ligand for carrying out the asymmetric synthesis or resolution of the racemates resides in the fact that intracomplex non-bonding interactions between the ligands may diminish due to *cis–trans* or *mer–fac* isomerism in addition to distortion of the metal–ligand bond angles. However, if in addition to the repulsive forces, interligand bonding interactions between the chiral inductor ligand and the functional groups of the other ligand are introduced into the complex, the possibilities for the chiral recognition of the enantiomers or prochiral groups of the other ligand become much greater.[4] A limiting case of such recognition is represented by chiral polydentate ligands, where chelate rings are additionally linked by a system of C–C and C–N bonds, and the asymmetric carbon centre in one chelate ring determines the chiral conformation of other chelate rings and their mutual spatial arrangement.[5] In earlier papers [6] we have shown that it is possible to use Cu^{II} complexes of tetradentate chiral Schiff bases formed from amino acids (aa) and either (*S*)-*o*-[(*N*-benzylprolyl)amino]benzaldehyde [(*S*)-bba] or (*S*)-*o*-[(*N*-benzylprolyl)amino]acetophenone [(*S*)-bap] to carry out the asymmetric synthesis of threonine with an enantiomeric purity of 98% and retroracemisation of the amino acids with an enantiomeric purity of up to 50%. In these complexes the chiral inducing moiety of (*S*)-proline is connected through the metal ion and the system of C–C and C–N bonds to the amino acid which under the action of a base undergoes various asymmetric transformations.[6] When the experiment is complete the complex is easily decomposed with an acid, the Schiff base itself is hydrolysed, and the amino acid is liberated. The isolated (*S*)-bba or (*S*)-bap may then be reused. To extend the synthetic possibilities of these systems, it is necessary to discover the interactions of which groups are responsible for the enantioselective effects observed in the complexes, as well as to elucidate the influence exerted by the nature of the central metal ion on these interactions and on the CH-acidity of the amino acid moiety. For the comparison to be useful, it is necessary that the metal ions give complexes with the same geometry. It is practically convenient to compare labile complexes of Ni^{II} and Cu^{II} which in the case of strong-field ligands yield square-planar complexes. Since such Ni^{II} complexes are diamagnetic, they offer an additional advantage: the ^{1}H n.m.r. technique is suitable for their conformational analysis.

In this paper we have studied quantitatively the comparative kinetic CH-acidity of the amino acids alanine (Ala), valine (Val), adamant-1-ylalanine (AdAla), and adamant-1-ylglycine (AdGly) and the enantioselective effects in Ni^{II} and Cu^{II} complexes of Schiff bases derived from (*S*)-bap and these amino acids. The resulting Schiff-base ligands differ in the bulk of the amino acid side-chain. Qualitative interpretation of the observed effects is given on the basis of the *X*-ray crystallographic studies of [Cu^{II}{(*S*)-bap-(*S*)-Val}] and [Ni^{II}{(*S*)-bap-(*S*)-Val}], as well as from the analysis of the

† (*S*)-2-{*o*-[(*N*-Benzylprolyl)amino]phenyl}ethylideneimino-3-methylbutanoato(2−)-*NN'N''*-nickel(II) and -copper(II) respectively.

Supplementary data available (No. SUP 23991, 30 pp.): elemental analyses, thermal parameters, full bond lengths and angles, H-atom co-ordinates, structure factors. See Instruction for Authors, *J. Chem. Soc., Dalton Trans.*, 1985, Issue 1, pp. xvii—xix.

For clarity metal complexes of Schiff bases [*e.g.* H_2-(*S*)-bap-(*S*)-Val] formed by the condensation of (*S*)-*o*-[(*N*-benzylprolyl)amino]-acetophenone [(*S*)-bap] and (*S*)-valine [(*S*)-Val] are represented by [M^{II}{(*S*)-bap-(*S*)-Val}].

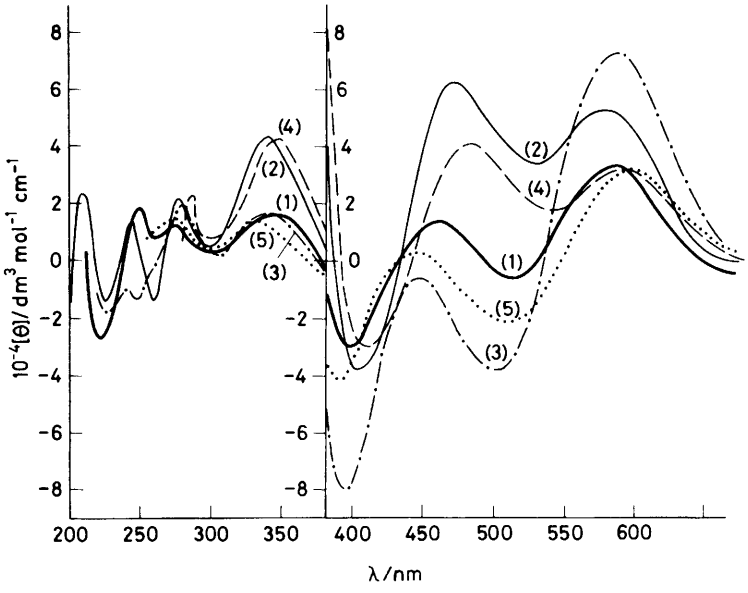


Figure 1. C.d. spectra of [Cu{(*S*)-bap-aa}] (in MeOH): aa = (1) Gly, (2) (*R*)-Val, (3) (*S*)-Val, (4) (*R*)-Ala, and (5) (*S*)-Ala. The right-hand side of the spectrum is expanded ten times (10^{-3}[θ])

200-MHz ^{1}H n.m.r. spectra of [Ni{(*S*)-bap-(*S*,*R*)-aa}] complexes. We also suggest ways for using these complexes to assign the absolute configurations of the amino acids.

Experimental

Materials.—Reagents were purchased from Reachim (U.S.S.R.), with the exception of (−)dibenzoyltartaric acid which was purchased from Merck. The isotopic purity of CD_3OD, $CDCl_3$, and D_2O was 99.2, 99.7, and 99.8% respectively; pure-grade $NiCl_2·6H_2O$, $Ni(O_2CMe)_2·4H_2O$, and $Cu(SO_4)·5H_2O$ were used without further purification. Sodium methoxide was prepared by dissolving metallic sodium in methanol under argon with cooling. (*R*,*S*)-β-(Adamant-1-yl)-α-aminopropionic acid, m.p. 236—239 °C (lit.,[7] 245 °C) and (*R*,*S*)-(adamant-1-yl)aminoacetic acid, m.p. 259—261 °C (lit.,[8] 260—262 °C) were prepared according to techniques described earlier.[8] (*S*)-*o*-[(*N*-Benzylprolyl)amino]acetophenone [(*S*)-bap] was prepared according to ref. 6*b*, m.p. 120—122 °C, α(578 nm, 25 °C, 1.0 g dm^{-3} in $CHCl_3$, *l* = 1 cm) = −112.75° [lit.,[6b] 115—116 °C, α (578 nm, 25 °C, 0.84 g dm^{-3} in $CHCl_3$, *l* = 5 cm) −110.71°]; (*S*)-*o*-[(*N*-benzylprolyl)amino]benzaldehyde [(*S*)-bba] was available from previous work.[6b]

Resolution of Adamant-1-ylglycine (AdGly).—The ester methyl (*R*,*S*)-(adamant-1-yl)aminoacetate, (*R*,*S*)-AdGly-(OMe), was prepared from (*R*,*S*)-AdGly on boiling in a mixture of methanol and thionyl chloride for 16 h, yield 92%. The free base was obtained by treating its hydrochloride suspension in $CHCl_3$ with NH_3.

The pure hydrochloride was obtained from the free base by passing HCl through its solution in diethyl ether, m.p. 268—270 °C (Found: C, 60.25; H, 8.20; N, 5.60. $C_{13}H_{22}ClNO_2$ requires C, 60.10; H, 8.50; N, 5.40%); i.r. (KBr): 1 745 cm^{-1} (C=O ester).

(*R*,*S*)-AdGly(OMe) (3.35 g, 0.015 mol) in anhydrous EtOH (5 cm^3) was added to a solution of (−)dibenzoyltartaric acid (6.1 g, 0.017 mol). After 10—12 h the precipitated salt (7.5 g) was filtered off, m.p. 165—169 °C, and recrystallized three times from EtOH to a constant m.p. of 199—200 °C, yield 1 g (17%) (Found: C, 64.30; H, 5.85; N, 2.25. $C_{29}H_{35}NO_{10}$ requires C, 64.05; H, 6.00; N, 2.40%). The salt was decomposed with 10% NaOH and (+)AdGly(OMe) extracted with diethyl ether in a yield of 92%; α(589.3 nm, 21 °C, 29 g dm^{-3} in EtOH, *l* = 10 cm) = +33.8°. The (+)AdGly(OMe) was then hydrolysed with a KOH solution in aqueous EtOH upon boiling for 4 h. After neutralisation (+)AdGly was isolated on a Dowex 50 × 8 column using 5% aqueous NH_3–MeOH (4 : 1) as eluant, yield of (+)AdGly, 82%; α[589.3 nm, 20 °C, 7 g dm^{-3} in MeOH–HCl (9 : 1), *l* = 10 cm].

Synthesis of Cu^{II} *Complexes of Schiff Bases derived from* bap *and Amino Acids.*—To bap (0.32 g 10^{-3} mol) in MeOH (10 cm^3), 1 mol dm^{-3} Na(OMe) (1.45 cm^3) in MeOH was added with stirring. A 0.4 mol dm^{-3} $Cu(SO_4)$ (2.72 cm^3) solution in water was then added, and after 5—10 min a solution of (*R*,*S*)-Ala (0.048 g, 1.1 × 10^{-3} mol) in 1 mol dm^{-3} Na(OMe) (1.1 cm^3) was also added. Stirring was continued for 3—4 h at room temperature under argon. The disappearance of the initial (*S*)-bap was monitored by t.l.c. On completion of the reaction, water and $CHCl_3$ were added to the mixture and the aqueous layer extracted several times with chloroform. The chloroform extracts were combined and evaporated. The resulting mixture of diastereomers (0.36—0.46 g, 80—100% yield) was separated chromatographically on silica gel using $CHCl_3$–Me_2CO (8 : 1), and each was additionally purified on an LH-20 column using C_6H_6–EtOH (3 : 1). Elemental analyses of all the complexes, with water of crystallization taken into account, correspond to those expected. The circular dichroism (c.d.) curves of the Cu^{II} complexes are presented in Figure 1. Melting points, molecular rotations, and electronic spectra of the synthesized complexes are presented in Table 1.

Synthesis of Ni^{II} *Complexes of Schiff Bases derived from either* (*S*)-bap *or* (*S*)-bba *and Amino Acids.*—Syntheses were carried out using the following general procedure for the Ni^{II} complexes of a Schiff base prepared from (*R*,*S*)-AdAla and (*S*)-bap. To (*S*)-bap (0.32 g, 1 × 10^{-3} mol) in absolute methanol (5 cm^3), $Ni(O_2CMe)_2·4H_2O$ (or $NiCl_2·6H_2O$), (0.25 g, 1 × 10^{-3} mol) and 0.65 mol dm^{-3} Na(OMe) (3 cm^3) were added and the mixture stirred for 10—15 min. A solution of (*R*,*S*)-AdAla (0.6 g, 2.7 × 10^{-3} mol) in 0.65 mol dm^{-3}

Table 1. Molecular rotations (25 °C),* melting points and electronic spectra of synthesized complexes

Complex	M.p./°C	M^{25}/° dm³ mol⁻¹ s⁻¹ 578 nm	546 nm	436 nm	364 nm	$\lambda_{max.}$/nm (log ε)
[Cu{(*S*)-bap-(*S*)-Ala}]	244—245	−170	−320	−70	+470	250 (4.41), 350 (3.63), 560 (2.07)
[Cu{(*S*)-bap-(*R*)-Ala}]	169—170	+1 340	+710	−660	+15 200	250 (4.25), 350 (3.45), 540 (2.15)
[Cu{(*S*)-bap-(*S*)-Val}]		−4 140	−6 800	−1 650	+14 900	252 (4.43), 360 (3.60), 580 (1.97)
[Cu{(*S*)-bap-(*R*)-Val}]		+2 100	+1 040	−720	+25 800	252 (4.33), 345 (3.54), 580 [1.82 (sh)]
[Ni{(*S*)-bap-(*S*)-Ala}]	276—277	+1 500	+1 170	+2 030	−14 000	260 (4.09), 320 (3.61), 395 (3.43), 515 (2.12)
[Ni{(*S*)-bap-(*S*)-Val}]	254—255	+11 900	+6 720	−2 820	−6 500	263 (4.33), 320 [3.45 (sh)], 400 (3.45), 525 (2.18)
[Ni{(*S*)-bap-(*R*)-Val}]	196—197	+1 060	+10 500	+14 800	−40 500	270 (4.79), 320 (3.70), 460 (5.42), 520 [2.00 (sh)]
[Ni{(*S*)-bap-Gly}]	210—211	+12 500	+11 000	+6 510	−22 800	325 (3.73), 395 (3.28), 520 [1.99 (sh)]
[Ni{(*S*)-bap-(*S*)-AdGly}]	236—237	+126	0	−10 200	+16 700	265 (4.16), 325 [3.57 (sh)], 400 (3.45), 540 (2.25)
[Ni{(*S*)-bap-(*R*)-AdGly}]	265—266	+7 140	+9 100	+16 700	+43 600	265 (4.11), 325 (3.66), 400 (3.42), 540 (1.48)
[Ni{(*S*)-bap-(*S*)-AdAla}]	132—133	+10 400	+2 600	−9 100	+1 170	263 (4.17), 320 [3.63 (sh)], 400 (3.44), 520 (2.13)
[Ni{(*S*)-bap-(*R*)-AdAla}]		+7 100	+10 900	−2 900	+5 400	260 [4.17 (sh)], 320 (3.71), 400 (3.42), 520 [2.22 (sh)]
[Ni{(*S*)-bba-(*S*)-Val}]	105—106	+9 610	+2 650	−2 150	+7 950	

* In methanol M^{25} does not depend on complex concentration.

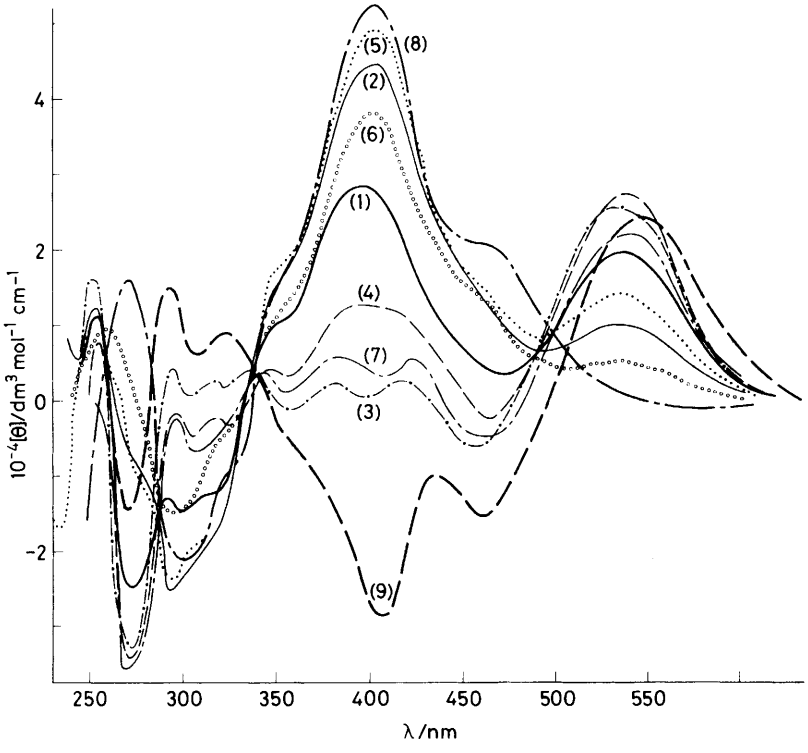


Figure 2. C.d. spectra of [Ni{(*S*)-bap-aa}] (in MeOH): aa = (1) Gly, (2) (*R*)-Val, (3) (*S*)-Val, (4) (*S*)-Ala, (5) (*R*)-Ala, (6) (*R*)-AdAla, (7) (*S*)-AdAla, (8) (*R*)-AdGly, and (9) (*S*)-AdGly

Na(OMe) (12 cm³) was then added with stirring. The reaction mixture was stirred for 20 h at 40—45 °C. After cooling the reaction mixture, water (50 cm³) was added, and the complex extracted with chloroform (3 × 30 cm³); the extract was washed with water, dried with sodium sulphate, and solvent removed *in vacuo*. The residue was chromatographed on silica gel (2 × 25 cm column), the eluant being CH_2Cl_2–Me_2CO (8 : 1): unreacted (*S*)-bap (0.04 g, 12%) (fraction I), [Ni{(*S*)-bap-(+)-AdAla}] (0.32 g, 55%) (fraction II), and [Ni{(*S*)-bap(−)-AdAla)}] (0.041 g, 6.8%) (fraction III) were isolated.

Other diastereomeric complexes were obtained under similar conditions, but using different reaction times (2—10 h) and different ratios of $CHCl_3$ and CH_2Cl_2–Me_2CO used for the chromatographic resolution. For the two diastereomers that which was faster moving contained enantiomerically pure (*S*)-amino acid, and that which was more strongly adsorbed on silica gel contained (*R*)-amino acid. All the complexes were additionally purified on LH-20 and dried *in vacuo* over P_2O_5. All the diastereomeric complexes had satisfactory elemental analyses, and their molecular weights in $CHCl_3$, determined by the vapour ebullioscopy technique, corresponded to expected values. Melting points, molecular rotations, and electronic data of the synthesized complexes are presented in Table 1. Proton chemical shifts of the synthesized Ni^{II} complexes run in CD_3OD solution are presented in Table 2. Figure 2 shows the c.d. spectra of the synthesized Ni^{II} complexes.

The [Ni{(*S*)-bba-(*S*)-Val}] was synthesized in accordance with the same technique, but 1.5 h was sufficient for the experiment.

Table 2. ^{1}H N.m.r. chemical shifts (δ/p.p.m.) for the complexes [Ni{(*S*)-bap-aa}] [a]

aa	Hᵅ (m, *n*H, *J*/Hz)	Me (m, *n*H, *J*/Hz)	CH_2(benzyl) (m, *n*H, *J*/Hz)	Me⟩=N (m, *n*H)
Gly	3.7, 4.2 (AB, 2 H, 15)		3.4, 4.3 (AB, 2 H, 12.5)	2.2 (s, 3 H)
(*S*)-Ala	4.1 (q, 1 H, 7)	1.9 (d, 3 H, 7)	3.3, 4.0 (AB, 2 H, 13)	2.3 (s, 3 H)
(*R*)-Ala	4.3 (q, 1 H, 7)	1.3 (d, 3 H, 7)	3.6, 4.0 (AB, 2 H, 14)	2.4 (s, 3 H)
(*S*)-Val	3.9 (d, 1 H, 3.5)	1.1 (d, 3 H, 6), 1.81 (m, 3 H)	3.3, 3.9 (AB, 2 H, 11)	2.5 (s, 3 H)
(*R*)-Val	4.1 (d, 1 H, 3.0)	1.0 (d, 6 H, 6)	3.1, 4.0 (AB, 2 H, 13)	2.4 (s, 3 H)
(*S*)-AdGly [b]	3.9 (s, 1 H)		3.3, 4.3 (AB, 2 H, 13)	2.4 (s, 3 H)
(*R*)-AdGly [b]	3.8 (s, 1 H)		4.0, 4.7 (AB, 2 H, 13)	2.3 (s, 3 H)
(*S*)-AdAla [b]	5.9 (m, 1 H)		3.3, 4.2 (AB, 2 H, 13)	2.4 (s, 3 H)
(*S*)-Val [c]	3.7 (d, 1 H, 3.5)	1.07 (d, 3 H, 6.6) 1.3 (d, 3 H, 6.5)	3.4, 4.1 (AB, 2 H, 13)	7.7 (m, 1 H) [d]

[a] 60 MHz in CD_3OD relative to $Me_3Si{-}O{-}SiMe_3$; the signals of the proline and phenyl fragments are 1.9—3.4 and 6.8—8.3 p.p.m. respectively. [b] Signals of adamantyl nucleus 1.5—2.0 p.p.m. [c] [Ni{(*S*)-bba-(*S*)-Val}] spectrum. [d] Aldimine hydrogen.

Isolation of Amino Acids from the Cu^{II} *and* Ni^{II} *Complexes.*—This is illustrated by the decomposition of [Ni{(*S*)-bap-(*S*)-Val}]. To 10% HCl (5 cm^3) a solution of the complex (6.23×10^{-2} g, 1.3×10^{-4} mol) MeOH (6 cm^3) was added with vigorous stirring for 20 min at 20—40 °C. Upon the disappearance of the red colour of the complex the reaction mixture was extracted with $CHCl_3$ (3×5 cm^3), aqueous NH_3 was added to pH 9, and the mixture again extracted with $CHCl_3$. The aqueous layer was transferred to a Dowex 50×8 column in the H^+ form. Elution was performed with 5% NH_3 [for AdAla and AdGly a mixture of 5% NH_3 and MeOH (4 : 1) was used]. The yield of the amino acid was 1.2×10^{-2} g (1.1×10^{-4} mol), *i.e.* 85%. The optical purity of Ala and Val was checked by gas-liquid chromatography.[9] For AdAla and AdGly polarimetry was used.

Preparation of Complexes from Ni^{II}, (*S*)-bap, *and* (*R,S*)-Ala *or* (*R,S*)-Val *in Solution in* MeOD.—The preparation was carried out in accordance with the conventional technique, the only exception being that all the constituents were first evaporated with D_2O. On completion of the reaction the products were transferred into a stirred mixture of $CHCl_3$ and D_2O. The chloroform solution containing the deuteriated diastereomers was evaporated, purified on LH-20, and the extent of the exchange of the α-hydrogen of the amino acid moiety was analyzed by using ^{1}H n.m.r. spectroscopy. Decomposition of the mixture of the deuteriated complexes gave (*S*)-2-[^{2}H]Ala and (*S*)-2-[^{2}H]Val with enantiomeric purities of 87 and 84% respectively.

X-*Ray Analysis.*—*Crystal data for* [Cu{(*S*)-bap-(*S*)-Val}]. $C_{25}H_{29}CuN_3O_3$, $M = 483.03$, orthorhombic, $a = 12.846(2)$, $b = 19.427(3)$, $c = 9.464(2)$ Å, $Z = 4$, $D_c = 1.376$ g cm^{-3}, space group $P2_12_12_1$, $F(000) = 1\,012$, $\mu = 15.8$ cm^{-1}, $T = 20$ °C. Crystals were obtained from aqueous ethanol. The unit-cell parameters and intensities of reflections were measured with a four-circle automatic Hilger and Watts diffractometer [Cu-K_α radiation, $\lambda = 1.541\,78$ Å, graphite monochromator, $\theta \leqslant 60°$, $\theta/2\theta$ scan, 1 670 independent reflections with $F^2 \geqslant 2\sigma$]. The structure was solved by the heavy-atom method and refined by least squares in a full-matrix anisotropic approximation. The hydrogen atoms of the Me groups were located in the difference synthesis; other H atoms were placed in geometrically calculated positions. The positional parameters of all the H atoms were refined in an isotropic approximation with a fixed value of $B_{iso.} = 5$ Å^2. The final refinement gave $R = 0.058$ ($R' = 0.054$). The absolute configuration of the proline fragment was determined by the Hamilton test, taking into account anomalous corrections for Cu, N, O, and C atoms (for the inverted structure $R = 0.064$ and $R' = 0.062$, which corresponds to the 99.5% probability of a true determination of the absolute configuration). The (*S*)-configuration of the valine fragment naturally coincides with that found in a number of its derivatives (*cf.*, for example, ref. 10). All calculations were carried out with the 'Eclipse S/200' minicomputer, using modified EXTL programs. Modification of the programs was carried out by A. I. Yanovskii and R. G. Gerr of this Institute. Atomic co-ordinates are given in Table 3. The crystal structure is shown in Figure 3.

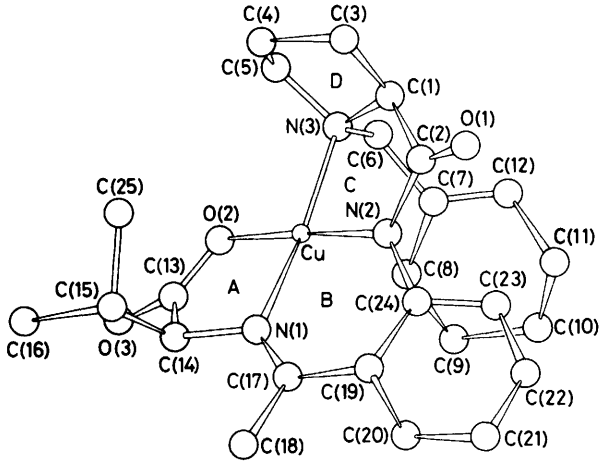


Figure 3. Structure of [Cu{(*S*)-bap-(*S*)-Val}]. Selected bond lengths: Cu–N(1), 1.950(6); Cu–N(2), 1.859(6); Cu–N(3), 1.999(7); and Cu–O(2), 1.925(4) Å

Crystal data for [Ni{(*S*)-bap-(*S*)-Val}]. $C_{25}H_{29}N_3NiO_3$, $M = 478.19$, orthorhombic, $a = 12.693(3)$, $b = 19.502(5)$, $c = 9.510(2)$ Å, $U = 2\,354$ Å^3, $D_m = 1.36$, $Z = 4$, $D_c = 1.35$ g cm^{-3}, space group $P2_12_12_1$, $F(000) = 1\,008$, $\mu = 15.8$ cm^{-1}, $T = 20$ °C. Crystals were obtained from a mixture of benzene and chloroform. The unit-cell parameters and intensities of reflections were measured with a Enraf-Nonius CAD-4 automatic diffractometer [spherical crystal; diameter 0.25 mm, Mo-K_α radiation, $\lambda = 0.710\,69$ Å, $\theta \leqslant 20°$, ω-scan, 1 408 independent reflections with $F^2 \geqslant 2\sigma$]. The structure was determined on a BESM-6 computer, using 'ROENTGEN-75' programs. The structure was solved by the heavy-atom method and refined by least squares in a block-diagonal anisotropic approximation (for non-hydrogen atoms). 24 Hydrogen atoms were located in the difference synthesis, the remainder were introduced from crystallochemical considerations. All the hydrogen atoms were refined in an isotropic approximation with the fixed value of $B_{iso} = 4$ Å^2. The final refinements

Table 3. Atomic co-ordinates of non-hydrogen atoms ($\times 10^4$) for [Cu{(*S*)-bap-(*S*)-Val}]

Atom	*x*	*y*	*z*
Cu	−471(1)	−1 511(1)	−1 331(1)
O(1)	−3 170(3)	−1 448(3)	−586(7)
O(2)	983(3)	−1 730(3)	−1 134(7)
O(3)	2 545(4)	−1 412(3)	−1 936(7)
N(1)	1(5)	−750(3)	−2 513(8)
N(2)	−1 876(5)	−1 353(3)	−1 725(7)
N(3)	−942(4)	−2 190(3)	121(8)
C(1)	−2 055(6)	−2 001(4)	468(11)
C(2)	−2 577(5)	−1 571(4)	−706(10)
C(3)	−2 007(9)	−1 623(6)	1 878(11)
C(4)	−888(7)	−1 534(6)	2 238(11)
C(5)	−385(7)	−2 171(5)	1 521(10)
C(6)	−827(8)	−2 902(4)	−459(10)
C(7)	−1 188(7)	−2 960(4)	−1 931(10)
C(8)	−477(8)	−2 858(5)	−3 088(11)
C(9)	−881(11)	−2 871(6)	−4 472(13)
C(10)	−1 951(11)	−2 987(6)	−4 720(14)
C(11)	−2 576(10)	−3 067(6)	−3 695(15)
C(12)	−2 237(8)	−3 067(5)	−2 159(14)
C(13)	1 561(6)	−1 317(4)	−1 756(9)
C(14)	1 122(5)	−638(4)	−2 208(10)
C(15)	1 305(6)	−61(5)	−1 116(12)
C(16)	2 450(9)	132(8)	−1 019(18)
C(17)	−526(5)	−402(4)	−3 427(9)
C(18)	−14(7)	204(5)	−4 162(13)
C(19)	−1 583(5)	−569(4)	−3 766(10)
C(20)	−2 025(7)	−288(4)	−5 012(11)
C(21)	−3 018(7)	−435(5)	−5 469(11)
C(22)	−3 547(7)	−903(5)	−4 759(13)
C(23)	−3 232(6)	−1 172(5)	−3 485(12)
C(24)	−2 268(5)	−1 023(4)	−2 958(10)
C(25)	866(8)	−273(6)	365(13)

Table 4. Atomic co-ordinates of non-hydrogen atoms ($\times 10^4$) for [Ni{(*S*)-bap-(*S*)-Val}]

Atom	*x*	*y*	*z*
Ni	578(1)	3 496(1)	1 471(1)
O(1)	3 609(5)	3 579(3)	855(8)
O(2)	−821(4)	3 250(3)	1 141(6)
O(3)	−2 467(4)	3 551(3)	1 656(8)
N(1)	36(5)	4 197(3)	2 573(7)
N(2)	1 956(5)	3 666(3)	1 914(7)
N(3)	1 071(5)	2 811(3)	139(7)
C(1)	2 192(7)	2 996(4)	−203(10)
C(2)	2 658(6)	3 435(5)	923(11)
C(3)	2 171(10)	3 354(7)	−1 638(13)
C(4)	1 033(9)	3 412(6)	−2 013(10)
C(5)	548(8)	2 820(5)	−1 240(8)
C(6)	980(7)	2 108(4)	824(10)
C(7)	1 378(9)	2 072(4)	2 267(10)
C(8)	696(11)	2 145(5)	3 376(12)
C(9)	1 090(17)	2 116(6)	4 750(14)
C(10)	2 197(18)	2 031(8)	4 956(16)
C(11)	2 849(14)	1 933(7)	3 830(17)
C(12)	2 455(12)	1 940(6)	2 508(14)
C(13)	−1 533(7)	3 666(4)	1 658(11)
C(14)	−1 080(6)	4 326(4)	2 225(10)
C(15)	−1 212(7)	4 914(5)	1 222(11)
C(16)	−2 367(10)	5 123(7)	1 153(17)
C(17)	525(7)	4 552(4)	3 537(9)
C(18)	−24(8)	5 155(5)	4 277(13)
C(19)	1 605(7)	4 404(5)	3 914(9)
C(20)	1 981(8)	4 690(5)	5 239(10)
C(21)	2 990(9)	4 536(5)	5 743(11)
C(22)	3 616(9)	4 083(5)	4 971(12)
C(23)	3 309(7)	3 826(5)	3 706(13)
C(24)	2 299(6)	3 970(4)	3 143(10)
C(25)	−796(11)	4 748(6)	−234(12)

gave $R = 0.057$. Atomic co-ordinates are given in Table 4. A projection of the molecule along the *c* axis is shown in Figure 4.

Deuterium Exchange of the α-Hydrogen in the Valine Fragment of [Ni{(*S*)-bap-(*S*)-Val}].—This was carried out directly in the ampoule of an n.m.r. spectrometer. To this end, 1.68×10^{-3} g of [Ni{(*S*)-bap-(*S*)-Val}] (3.5×10^{-5} mol) was dissolved in 0.87 mol dm^{-3} Na(OMe) (0.5 cm^3) and kept for 6 d at 24 °C. After the disappearance of the signal from the α-hydrogen of the valine fragment, the complex was subjected to decomposition, and 2-[^{2}H]Val was isolated by conventional techniques. The (*S*)-2-[^{2}H]Val contained not more than 3% of 2-[^{1}H]Val, and its enantiomeric purity was 84%.

Epimerisation of the Complexes under the Effect of MeO^-.—This was carried out as illustrated for the epimerisation of [Cu{(*S*)-bap-(*S*)-Val}] and [Cu{(*S*)-bap-(*R*)-Val}]. A flask containing a solution of the diastereomeric complex (7×10^{-3} g) in 0.1 mol dm^{-3} Na(OMe) (under argon) was placed in a thermostat at 25 °C. Part of the solution was transferred into the polarimeter cell, and the optical rotation *versus* time variation was monitored at 546 nm (for the diastereomeric Ni^{II} complexes, at 436 nm). After the optical rotation ceased changing, the contents of the flask were either neutralised with 0.1 mol dm^{-3} HCl and the amino acid was isolated as described above, or they were transferred into a vigorously stirred mixture of $CHCl_3$ and water. The chloroform layer was separated, and the ratio of the diastereomers was analysed by t.l.c. The other diastereomer was also epimerised in this way. Both diastereomers gave an equilibrium mixture, irrespective of the epimerisation conditions and the analysis technique, containing the same ratios of the (*S*)- and (*R*)-enantiomers of the amino acids. The results of the epimerisation experiments are presented in Table 5.

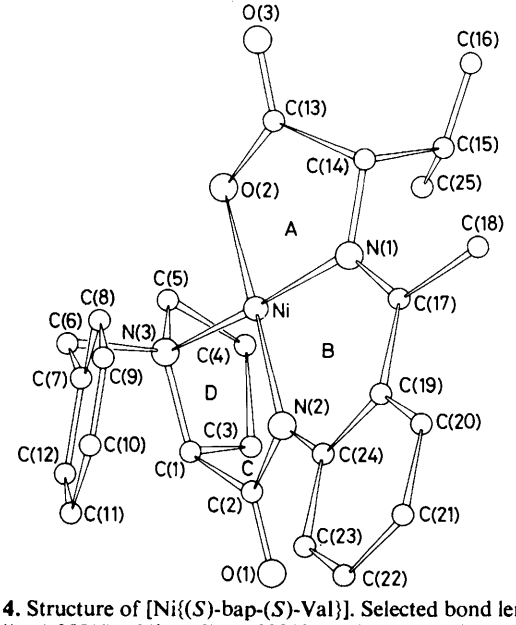


Figure 4. Structure of [Ni{(*S*)-bap-(*S*)-Val}]. Selected bond lengths: Ni–N(1), 1.855(6); Ni–N(2), 1.829(6); Ni–N(3), 1.943(7); and Ni–O(2), 1.866(5) Å

Table 5. Epimerisation rate constants for the amino acid fragments in Ni^{II} and Cu^{II} complexes of Schiff bases from (*S*)-bap and (*S*)-bba and the ratio of diastereomers in equilibrium mixtures [a]

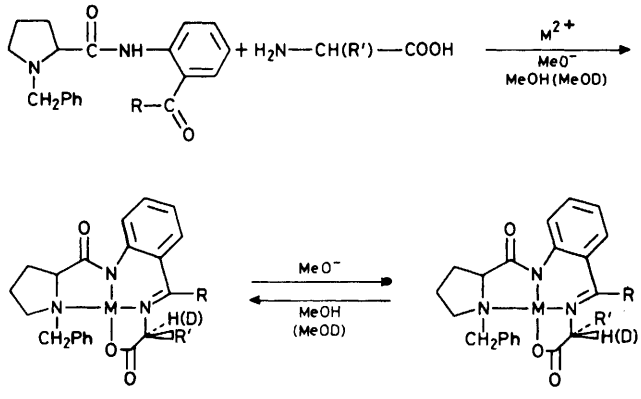
No.	Compound	$k_{ep.}/s^{-1}$ ($k_{ep.}/dm^3\ mol^{-1}\ s^{-1}$) [b]	$[OMe^-]$/mol dm^{-3}	Ratio of diastereomers in equilibrium [c]
1	[Cu{(*S*)-bap(*S*,*R*)-Ala}]	4×10^{-4} (4.7×10^{-2})	0.012	65 : 35
2	[Cu{(*S*)-bap-(*S*,*R*)-Val}]	5.9×10^{-4} (1.8×10^{-3})	0.33	69 : 31
3	[Cu{(*S*)-bap-(*S*,*R*)-Val}]	1.5×10^{-4} (1.5×10^{-3})	0.1	65 : 35 [d]
4	[Ni{(*S*)-bap-(*S*,*R*)-Ala}]	1.3×10^{-3} (1.2×10^{-1})	0.012	91 : 9 (93.4 : 6.6) [e]
5	[Ni{(*S*)-bap-(*S*,*R*)-Val}]	1.64×10^{-4} (5×10^{-4})	0.33	88 : 12 (88 : 12) [f]
6	[Ni{(*S*)-bap-(*S*,*R*)-AdAla}]	2.6×10^{-4} (8×10^{-4})		76 : 24 [f]
7	[Cu{(*S*)-bba-(*S*,*R*)-Ala}]		0.33	50 : 50 [g]
8	[Cu{(*S*)-bba-(*S*,*R*)-Val}]	9×10^{-3} (9×10^{-2})	0.1	80 : 20 [g]
9	[Ni{(*S*)-bba-(*S*,*R*)-Ala}]			57.5 : 42.5 [e]
10	[Ni{(*S*)-bba-(*S*,*R*)-Val}]			89.2 : 10.8 [e]

[a] At 25 °C in MeOH; concentration of complexes is (5—25) $\times 10^{-3}$ mol l^{-1}. [b] Mean value of epimerisation rate constant for two diastereomers. Determination error 10—15%. [c] Determined by g.l.c. from the ratio of the enantiomers of the amino acids after decomposition of the equilibrium mixture of diastereomers. Equilibrium was attained starting from both diastereomers. Reproducibility within 5%. [d] From polarimetric data for the equilibrium mixture of diastereomers. [e] After complete exchange of the α-proton of the amino acid fragment in CD_3OD (according to ^1H n.m.r. data). [f] Ratio of diastereomers as determined by t.l.c. [g] Ref. 6*b*.

Physical Measurements.—Proton n.m.r. spectra were recorded on a TESLA NMR-BS-467A (60 MHz) or Brucker WP-200 (200 MHz) spectrometer; the signals were assigned by using a double resonance technique. C.d. spectra were recorded on a Jasco J-20 and electronic spectra on a Specord u.v.–visible spectrophotometer. Specific rotations were measured on a Perkin-Elmer-241 polarimeter. Molecular weights were determined on an EP-75 instrument.

Kinetic measurements were carried out in a thermostatted cell of a polarimeter. The concentration of samples was the same as in the epimerisation experiments. The rate constants of the processes were calculated from the conventional formula for pseudo-first-order reactions.[11]

Calculation of vicinal contributions to the observed c.d. spectrum was carried out in the usual manner, see ref. 12.



[M(bap–Ala)]; M = Cu or Ni; R = Me; R' = Me
[M(bap–Val)]; M = Cu or Ni; R = Me; R' = Pr^i
[M(bap–Gly)]; M = Ni; R = Me; R' = H
[M(bap–AdGly)]; M = Ni; R = Me; R' = Ad
[M(bap–AdAla)]; M = Ni; R = Me; R' = CH_2Ad
[M(bba–Val)]; M = Ni; R = H, R' = Pr^i

Scheme. Preparation of [M(bap-aa)] and [M(bba-aa)] complexes

Results

Synthesis and Structure of Ni^{II} *and* Cu^{II} *Complexes of Schiff Bases prepared from Amino Acids and* (*S*)-bap *and* (*S*)-bba.—(*S*)-bap and (*S*)-bba interact in MeOH with Cu^{II} or Ni^{II} ions and aa to give a mixture of orange diastereomeric complexes according to the Scheme.

The structure of the complexes [Cu{(*S*)-bba-(*S*)-aa}] (aa = Val, Gly, or threonine) has already been established on the basis of physical and chemical data.[6b] However, in contrast to the (*S*)-bba complexes, (*S*)-bap complexes are obtained at higher pH, thus epimerisation of an amino acid fragment accompanies the reaction. Thus, irrespective of whether (*S*)-, (*R*)-, or (*S*,*R*)-aa have initially been used for the reaction, the resulting Cu^{II} complexes have the same c.d. spectrum, and decomposition of the complexes in all cases gives (*S*)-Ala with 30% enantiomeric purity. The same applies for the diamagnetic Ni^{II} complexes (with the exception of AdGly). Their preparation in Na(OMe) solution in MeOD at 40 °C according to the conventional technique (10—15 h) gives complexes containing only 2-[^{2}H]aa. The use of the initial (*R*,*S*)-Ala gives a complex containing 93% (*S*)-2-[^{2}H]Ala and 7% (*R*)-2-[^{2}H]Ala. After extracting the complex with chloroform, racemic Ala remains in solution. The diastereomeric Ni^{II} and Cu^{II} complexes are easily separated by preparative chromatography on silica gel. Their structure has been established by analogy with the (*S*)-bba complexes.[6b] The various physical data given in Figures 1 and 2 and Tables 1 and 2 demonstrate that all the synthesized complexes have the structure shown in the Scheme and differ only in the structure and configuration of the amino acid fragment.

Figures 3 and 4 show the structures of the complexes [Cu{(*S*)-bap-(*S*)-Val}] and [Ni{(*S*)-bap-(*S*)-Val}] respectively. As in the structure of bis[*N*-benzyl-(*S*)-prolinato]copper(II) investigated earlier,[13] the copper atom has a square-planar co-ordination with a considerable tetrahedral distortion. Displacements of the atoms N(1), N(2), N(3), and O(2) from the mean plane CuN(1)N(2)N(3)O(2) are on average 0.13 Å. The Cu–O(2) bond length of 1.925(4) Å is usual for complexes of copper with amino acids (*cf.*, for example, ref. 14). In ring A the atom C(14) is displaced by 0.41 Å from the plane CuO(2)C(13)N(1) (planar to within 0.04 Å). Such a conformation of ring A makes the atom C(25) of the axial isopropyl group approach the Cu atom at a distance of 3.36(1) Å. A similar close contact [3.27(1) Å] is also observed in bis[*N*-benzyl-(*S*)-valinato]copper(II) trihydrate.[15] The nitrogen atom N(3) adopts the (*R*)-configuration as in the earlier investigated

complex [Cu{(*S*)-bap-Gly}][6b] and in other *N*-benzylprolyl complexes.[13] The co-ordination of N(3) to copper in all the Cu complexes is confirmed by the observed c.d. spectra of [Cu{(*S*)-bap-Gly}] and comparison of its calculated spectrum obtained on the basis of the spectra of other [Cu{(*S*)-bap-(*S*)-aa}] and [Cu{(*S*)-bap-(*R*)-aa}] complexes. The benzyl group and the alkyl group of the amino acid in the complexes [Cu{(*S*)-bap-(*S*)-aa}] lie on opposite sides of the co-ordination plane; the phenyl ring of the benzyl group effectively screens the Cu atom from the side of the second apical position, and thus square-pyramidal or octahedral co-ordination becomes impossible.

In the structure of [Ni{(*S*)-bap-(*S*)-Val}] the nickel atom has a square-planar co-ordination with a slight tetrahedral distortion: the displacement of the atoms N(1), N(2), N(3), and O(2) from the mean plane N(1)N(2)N(3)O(2) is close to ±0.09 Å. In ring A the atom C(14) is displaced by 0.39 Å from the plane O(2)C(13)N(1) (planar to within ±0.04 Å). The atom C(25) of the isopropyl group lies 3.4(1) Å from Ni. The torsion angle NiN(3)C(6)C(7) which characterizes the orientation of the benzyl group in relation to the Ni atom is 46.0°. The atom N(3) acquires the configuration (*R*).

Kinetic CH-*acidity of the Amino Acid Moiety in* [M{(*S*)-bap-aa}] *and* [Ni{(*S*)-bba-(*S*)-Val}].—As has been stated above, the Cu^{II} and Ni^{II} complexes epimerise in the course of their synthesis, and the α-protons of the amino acid moiety are easily exchanged by deuterium. Thus, for example, both *pro-S* and *pro-R* hydrogens of the glycine fragment in [Ni{(*S*)-bap-Gly}] are exchanged in CD_3OD solution under the action of 0.5 mol dm^{-3} 1,4-diazabicyclo[2.2.2]octane during 8 h at 25 °C at similar rates. The deuterium exchange of the α-hydrogen of (*S*)-Val in [Ni{(*S*)-bap-(*S*)-Val}] proceeds under the action of 0.83 mol dm^{-3} $Na(OCD_3)$ in CD_3OD during several days at 25 °C. The epimerisation of the complexes under the action of MeO^- is accompanied by a change in the optical rotation, which can be described in terms of the first-order kinetics. The proline fragment of the complexes is not affected. Thus, (*S*)-bap isolated after epimerisation in each case had a specific rotation identical to that of the initial (*S*)-bap. The c.d. spectrum of an equilibrium mixture of diastereomers coincided with the theoretically calculated one assuming that the (*S*)-proline fragment does not epimerise and the mixture consists of [M{(*S*)-bap-(*S*)-aa}] and [M{(*S*)-bap-(*R*)-aa}].

Table 5 lists the first-order rate constants of the epimerisation reactions under the action of MeO^-. The second-order rate constants calculated assuming first-order dependence on $[MeO^-]$ are also given in Table 5. Comparison of the calculated second-order rate constants for the epimerisation of [Cu{(*S*)-bap-(*S*)-Val}] in 0.33 and 0.1 mol dm^{-3} MeO^- shows that such an assumption is valid in the first approximation (Table 5, runs 2 and 3). As can be seen from runs 3 and 8, the lability of the α-proton of the amino acid fragment in [Cu{(*S*)-bba-(*S*)-Val}] (or [Cu{(*S*)-bba-(*R*)-Val}]) is 60 times that in [Cu{(*S*)-bap-(*S*)-Val}] (or [Cu{(*S*)-bap-(*R*)-Val}]). An increase in the bulk of the amino acid fragment diminishes the lability of the α-proton both in the Cu^{II} and Ni^{II} complexes. Thus, for [Cu{(*S*)-bap-(*R*,*S*)-Ala}] the rate constant of the process is greater than for [Cu{(*S*)-bap-(*R*,*S*)-Val}] by a factor of 26 (runs 1 and 2). Going from [Ni{(*S*)-bap-(*R*,*S*)-Ala}] to [Ni{(*S*)-bap-(*R*,*S*)-Val}] slows down the process by a factor of 240 (runs 4 and 5). In the case of the complex [Ni{(*S*)-bap-(*R*,*S*)-AdGly}], epimerisation does not occur even in 0.8 mol dm^{-3} MeO^- during 24 h at 25 °C.

Enantioselective Effects in [Cu{(*S*)-bap-aa}] *and* [Ni{(*S*)-bap-aa}].—Table 5 presents the ratios of the diastereomers of the complexes, determined in an equilibrium mixture. The results are the same, irrespective of whether this equilibrium is attained from the diastereomer containing (*S*)-aa or (*R*)-aa. Denoting the amino acid fragment as (*S*,*R*)-aa in Table 5 means that the equilibrium has been attained starting from both diastereomers and the mean value is given in the Table. Irrespective of the method by which the ratio of the diastereomers is determined, the result is the same (see runs 2, 3, and 5). The data presented show that both (*S*)-bba and (*S*)-bap complexes of Ni^{II} have greater enantioselective effects than the Cu^{II} complexes. Thus, for example, going from [Cu{(*S*)-bap-(*S*,*R*)-Ala}] to [Ni{(*S*)-bap-(*S*,*R*)-Ala}] results in an increase of the excess of the (*S*)-Ala-containing diastereomer from 30 to 82% (see Table 5, runs 1 and 4). For the Val complexes, the diastereomer excess increases from 30—40 to 76% (runs 2, 3, and 5). In the (*S*)-bba complexes the increase of the enantioselective effects is also observed when going from Cu^{II} to Ni^{II}. The excess of the diastereomer containing (*S*)-Val in the Cu^{II} and Ni^{II} complexes is 60 and 80% respectively (runs 8 and 10). For the (*S*)-bba complexes an increase in the bulk of the alkyl side-chain of the amino acid fragment leads to an increase in the excess of the (*S*)-aa containing diastereomer both for the Cu^{II} and Ni^{II} complexes (runs 7—10), but in the (*S*)-bap complexes an inverse dependence of the enantioselective effects on the bulk of the amino acid side-chain is observed. Thus, the diastereomeric excess in the case of the Ni^{II} complexes in the series Ala, Val, and AdAla drops in the order 80, 76, and 52% (runs 4—6); almost no dependence is observed for the complexes of (*S*)-bap with Cu^{II} and aa (runs 1—3).

The observed stereoselective effects and the characteristic c.d. spectra of the Ni^{II} complexes make it possible to assign the configuration of the α-amino acids, which has not been possible before. The vicinal components of the c.d. spectra of the synthesized complexes are presented in Figure 5. For the amino acids with known (*S*)-configuration [(*S*)-Ala and (*S*)-Val] the positive Cotton effect at 530—560 nm is followed by negative Cotton effects at 450 and 400 nm. The vicinal contributions of (+)AdAla and (+)AdGly in the complexes of Ni^{II} and (*S*)-bap are also presented in this Figure. These data furnish convincing evidence that both amino acids belong to the (*S*)-aa series. Hydrochlorides of the amino acids,

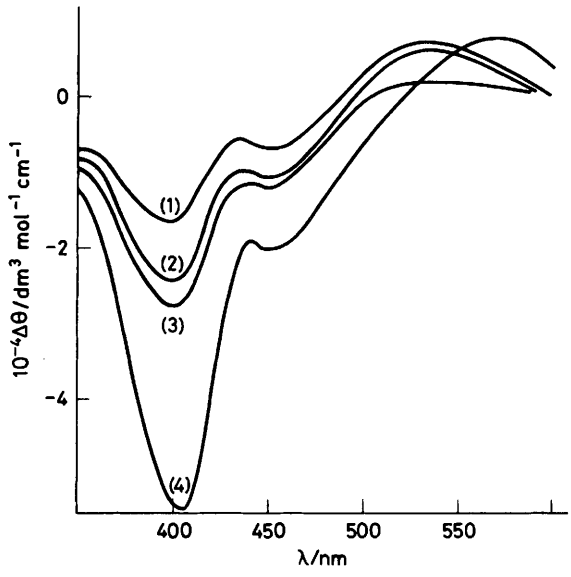


Figure 5. Vicinal contribution of (*S*)-amino acids in the c.d. spectra of [Ni{(*S*)-bap-aa}]: aa = (1) (*S*)-Ala, (2) (*S*)-Val, (3) (*S*)-AdAla, and (4) (*S*)-AdGly

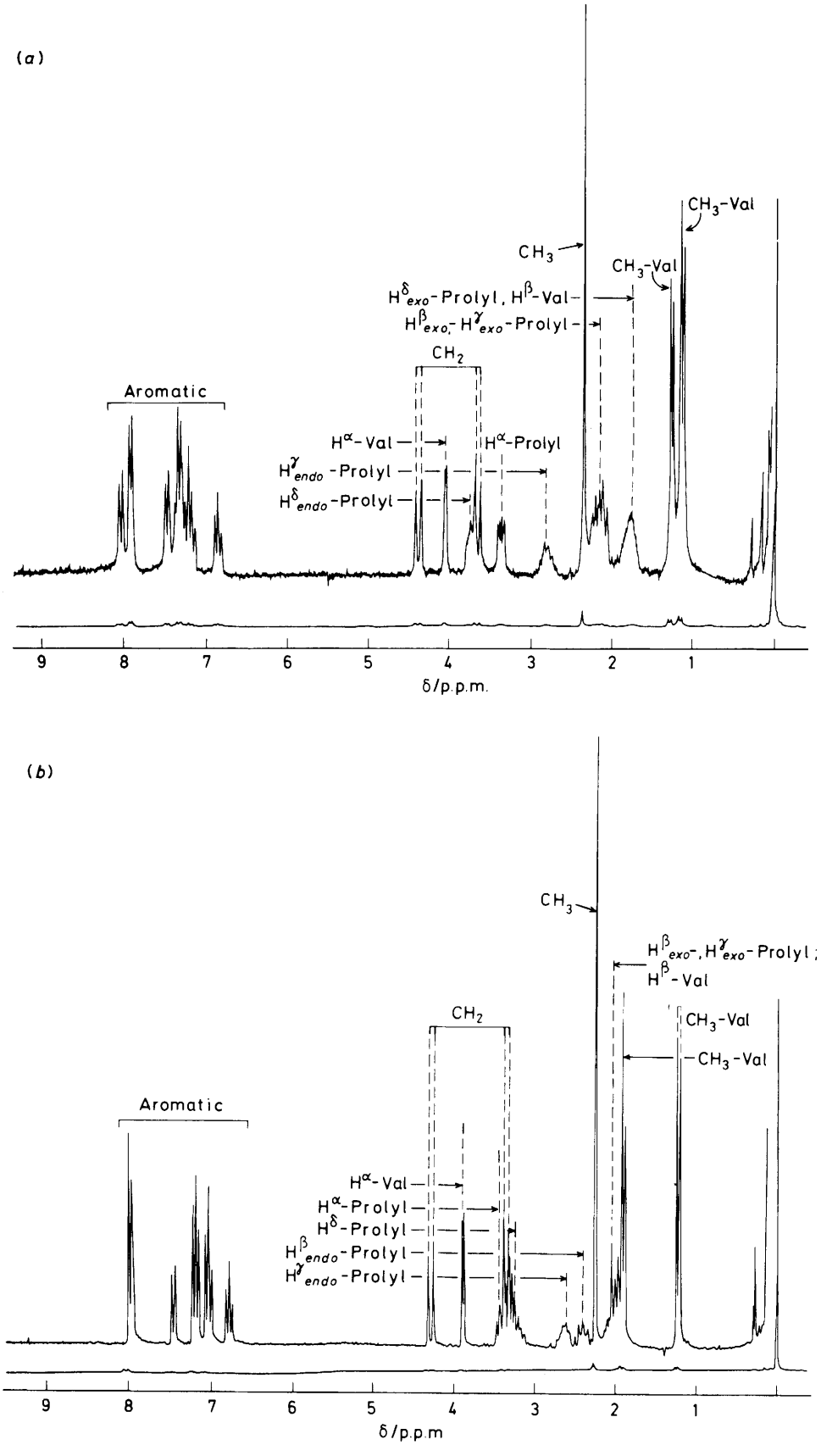


Figure 6. 200-MHz ^1H N.m.r. spectra ($CDCl_3$) of [Ni{(*S*)-bap-aa}]complexes (relative to $Me_3Si{-}O{-}SiMe_3$): (*a*) aa = (*R*)-Val, and (*b*) aa = (*S*)-Val

isolated from these complexes gave optical rotations for AdAla of α[589.3 nm, 20 °C, 8 g dm^{-3} in MeOH–HCl (9 : 1), l = 2 cm] +15.6° [lit.,[7] AdAla·HCl: α(589,3 nm, 20 °C ,10 g dm^{-3} in MeOH) = +16.2°] and for AdGly of +14°. Earlier AdAla, having a positive rotation in MeOH–2 mol dm^{-3} NH_3 (1 : 1), on the basis of indirect data, had been assigned the (*S*) configuration;[7] this is in complete agreement with our conclusions. An additional argument in favour of this assignment is the observed enantioselectivity of the AdAla epimerisation in the complex of Ni^{II} with bap (Table 5, run 6) and the chromatographic behaviour of the diastereomers. As in the case of other (*S*)-amino acids, the isomer less strongly adsorbed on silica gel is formed in excess. As might be expected, (+)AdAla was obtained from this isomer. Diastereomeric complexes of AdGly could not be epimerised under our experimental conditions. Nevertheless, from (+)AdGly we only obtained the less strongly adsorbed diastereomer as in all the other [Ni{(*S*)-bap-(*S*)-aa}] complexes.

Discussion

The formation of metal Schiff-base complexes of amino acids with bba or bap leads to a macrocyclic structure (see Figures 3 and 4) in which the chiral proline fragment induces chiral distortions of the chelate rings. Thus, in [Cu{(*S*)-bap-Gly}], whose structure was investigated earlier,[6b] the five-membered ring of the glycine fragment has an envelope conformation with the Cu atom displaced by 0.15 Å from the O,C,C,N plane; the six-membered metallacycle is a distorted boat with the C and N atoms forming the aldimine bond displaced by 0.1 and 0.3 Å respectively from the plane of the other atoms of the ring. In [Cu{(*S*)-bap-(*S*)-Val}] and [Ni{(*S*)-bap-(*S*)-Val}], which differ from the Gly complex by the replacement of the *pro-S* hydrogen with an isopropyl group, the distortions of the rings are enhanced. Evidently, interaction of the isopropyl group of the amino acid fragment with the methyl group of the acetophenone fragment brings about an additional distortion of the metalla-rings and makes the isopropyl group of the Val fragment occupy a pseudo-axial position. The same interaction is, evidently, also responsible for rotamer distribution with '*gauche*' spatial arrangement of the α- and β-hydrogens and the torsion angles equal to 62° for both the Cu^{II} and Ni^{II} complexes. Such a conformation of the isopropyl group causes the methyl group, C(25), to be directly above the metal ion. That this orientation is preserved in solution as well as in crystals can be deduced from the ^1H n.m.r. spectra of [Ni{(*S*)-bap-(*S*)-Val}] in CD_3OD (see Table 2) and in $CDCl_3$ (see Figure 6). These data show that the signal (A_3B) of one of the diastereotopic methyl groups of the valine fragment is found in an unusually weak field at 1.8 (CD_3OD) or 1.9 p.p.m. ($CDCl_3$). It was shown earlier that metals with a d^8 electronic configuration in square-planar complexes magnetically deshield the hydrogens of alkyl groups located above the coordination plane.[16] The *gauche* conformation of the isopropyl group in solution is confirmed by the constant $J_{vic}(H^{\alpha}-H^{\beta})$ = 3 (CD_3OD) or 3.4 Hz ($CDCl_3$). Assuming J_T (*anti*) and J_G (*gauche*) to be 13.3 and 2.4 Hz,[17a] the proportion of the *gauche* conformation for the free-rotating isopropyl group is 90%. For the case of hindered rotation of the isopropyl group using the Carplus correlation,[17b] the calculated dihedral angle between the α- and β-hydrogens coincides with that found by *X*-ray analysis. In [Ni{(*S*)-bba-(*S*)-Val}] the signals of the methyl protons of the isopropyl group are rather upfield [1.3 and 1.07 p.p.m. (Table 2)], this, evidently, being due to less pronounced axial orientation of the isopropyl group, although the content of the *gauche* conformer is still high (J_{vic} = 3.5 Hz). A less pronounced axial orientation is associated with a smaller steric interaction between the alkyl group of the amino acid and the aldimine proton in the complexes of (*S*)-bba compared with the methyl group of the acetophenone fragment in the complexes of (*S*)-bap.

It is obvious that the formation of the planar amino acid carbanion fragment in epimerisation, which requires flattening of the α-carbon, must lead to severe repulsive steric interactions between the amino acid side-chain and the methyl group of the acetophenone fragment.[18] This fact, evidently, explains the deceleration of the epimerisation rate constants with increasing bulk of the amino acid side-chain. This trend is stronger in the case of the Ni^{II} than the Cu^{II} complexes because of the greater energy of the Ni–O and Ni–N bonds compared with similar bonds in the Cu^{II} complexes (see Figures 3 and 4). A relatively more rapid increase of the bond energies with increasing ligand strength for Ni^{II} (d^8) compared with Cu^{II} (d^9) is a well known phenomenon.[19] An increased bond strength makes the chelate rings more rigid and renders the minimisation of the intracomplex steric non-bonding interactions more difficult. Hence, greater stereoselective effects are observed in the Ni^{II} complexes than in the Cu^{II} complexes (see Table 5). The origin of enantioselective effects in these complexes is determined by the difference in the energy of orientation of the amino acid side-chain towards the benzyl group or towards the *endo*-hydrogens of the proline fragment. The steric strain is already sufficiently large in the energetically favourable isomers of [M{(*S*)-bap-(*S*)-aa}] (see Figures 3 and 4). The methyl group of the valine fragment [C(25)] and the metal ion in both the Ni^{II} and Cu^{II} complexes are brought closer together. Using Pauling's approach,[20] it is possible to evaluate the van der Waals radius of Ni^{II} and Cu^{II} as being approximately 2 Å, this being equal to the radius of the methyl group also.[21] The observed distance of C(25)–metal ion (3.41 Å for Ni^{II} and 3.36 Å for Cu^{II}) is thus smaller or equal to the sum of their van der Waals radii (4 Å).

The phenyl ring of the benzyl group, which shields the metal atom, is also closer to it than the sum of the van der Waals radii (3.8 Å). Furthermore, the distances of the proline ring hydrogens H^{γ}_{endo} or H^{δ}_{endo} from Cu are 3.08 Å, this being close to the sum of van der Waals radii (3.2 Å). In other words, the metal atom is sandwiched between the methyl group of the isopropyl fragment and the hydrogens of the proline moiety on one side and the phenyl ring of the benzyl group on the other side. Such an orientation of the benzyl group in addition to the possible factors of metal–phenyl attraction [17,22] is a consequence of a repulsion of the phenyl ring and the hydrogens of the proline fragment. In the less energetically favourable isomers of [M{(*S*)-bap-(*R*)-Val}] there arise additional interactions. One such interaction may be a repulsion between the alkyl group of the amino acid and the benzyl group of the proline fragment. Such interaction leads to an increase in the proportion of the conformer with the phenyl ring of the benzyl group turned away from the metal ion and/or to the displacement of the isopropyl group of the (*R*)-valine fragment from the axial orientation.

Figure 6 shows the ^1H n.m.r. spectra (200 MHz) of [Ni{(*S*)-bap-(*S*)-Val}] and [Ni{(*S*)-bap-(*R*)-Val}] in $CDCl_3$. As can be seen in this Figure, the signals of the Pr^i methyl groups in the isomer containing (*R*)-Val are actually found at 1.3 and 1.2 p.p.m. instead of 1.93 and 1.25 p.p.m. for the diastereomer with (*S*)-Val. This upfield shift is in agreement with the receding of the Pr^i group from the Ni^{II} atom in the case of the (*R*)-Val diastereomer although $J_{vic}(H^{\alpha}H^{\beta})$ corresponds to the 90% *gauche* conformation as in the isomer with (*S*)-Val. The spectra of the diastereomers differ significantly in the region where the signals due to the proline fragment hydrogens are located. The signals H^{δ}_{exo} and H^{δ}_{endo} for the (*S*)-Val isomer are at 3.3 p.p.m., and for the (*R*)-Val isomer are at 1.8 and 3.8 p.p.m. The upfield shift of the H^{δ}_{exo} signal for the isomer

[Ni{(*S*)-bap-(*R*)-Val}] is caused by the magnetic shielding of the phenyl ring, since in this isomer the population of the conformer with the benzyl group situated over the proline fragment is increased. Down-field shift of the signals H^{δ}_{endo} (0.5 p.p.m.) and H^{γ}_{endo} (0.4 p.p.m.) is a consequence of a distortion of the proline ring in the (*R*)-Val isomer, which results in the H^{δ}_{endo} and H^{γ}_{endo} being brought closer to the Ni^{II} atom. Such a distortion is a result of a steric repulsion of the alkyl and benzyl groups in this isomer and of a subsequent change in the conformation of the pyrrolidine ring. Thus, the interaction of the side-chain of the amino acid and the benzyl substituent is one of the factors responsible for the observed enantioselectivity in the series of the [M{(*S*)-bap-(*R*,*S*)-aa}] complexes. Confirmation of this is found in a sharp decrease of the asymmetric yield of threonine in the condensation of acetaldehyde with a Cu^{II} complex of a glycine Schiff base with (*S*)-*o*-(prolyl)aminoacetophenone, as compared with the corresponding *N*-benzylated complex.[6a]

In contrast to mixed-metal complexes of (*S*)-*N*-benzylproline and (*R*,*S*)-amino acids,[23] where both ligands are linked only through the metal ion, in the system studied here the ligands are linked both through the metal ion and the rigid framework of the covalent bonds of the entire system of the Schiff base. Therefore, minimisation of the intracomplex steric interactions in such a system is hindered, and this leads to considerable enantioselective effects.

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