

UNIVERSITE DE NEUCHÂTEL
FACULTE DES SCIENCES

**SYNTHESE DE NOUVEAUX LIGANDS
OPTIQUEMENT ACTIFS DE TYPE TRIAMINE.
FORMATION ENANTIOSELECTIVE DE LA
PHENYLALANINE PAR ISOMERISATION
D'UNE BASE DE SCHIFF EN PRESENCE DE
CUIVRE(II) ET DE CES LIGANDS.**

Forme réduite de la thèse présentée à la Faculté des Sciences par

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pour l'obtention du grade de docteur ès sciences*

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IMPRIMATUR POUR LA THÈSE

Synthèse de nouveaux ligands optiquement
actifs de type triamine. Formation énantio-
sélective de la phénylalanine par isomérisa-
tion d'une base de Schiff en présence de
cuivre(II) et de ces ligands
de Monsieur Thierry Chuard

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La Faculté des sciences de l'Université de Neuchâtel
sur le rapport des membres du jury,

MM. et Mme les professeurs K. Bernauer,
R. Deschenaux, H. Stoeckli-Evans, R. Neier
et C.W. Schläpfer (Fribourg)

autorise l'impression de la présente thèse.

Neuchâtel, le 27 juillet 1992

Le doyen :



A. Robert

*C'est au pied du mur,
que l'on voit le mieux le mur ...*

J.M. Bigard

A mes parents

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Enantioselective Formation of Amino Acids by Isomerization of Mixed Ligand Copper(II) Schiff-Base Complexes [1]

Thierry Chuard [2], François Gretillat, and Klaus Bernauer*

Abstract. The formation of optically active phenylalanine from phenylpyruvic acid and pyridoxamine in the presence of various chiral Cu^{II} complexes was investigated as a function of the reaction conditions. The enantioselectivity of the reaction, as well as the pH- and ligand-dependant racemization of the product, is discussed in terms of possible reaction pathways and the most likely structure of intermediate [Cu(L)aldimine] complexes.

Scheme 1

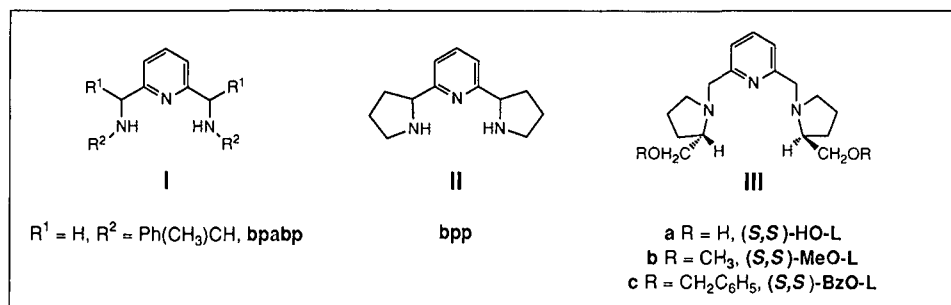
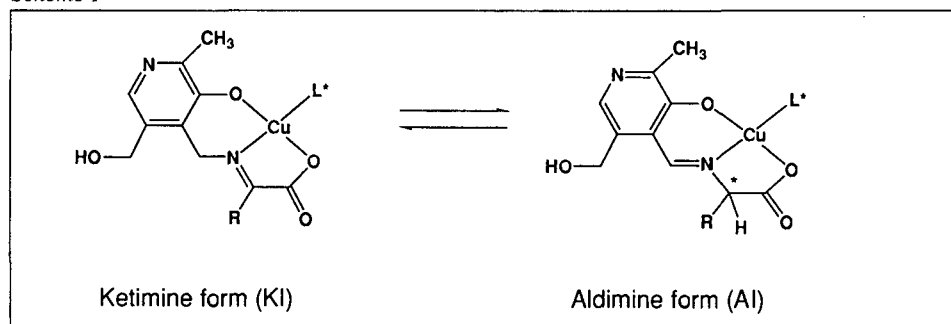
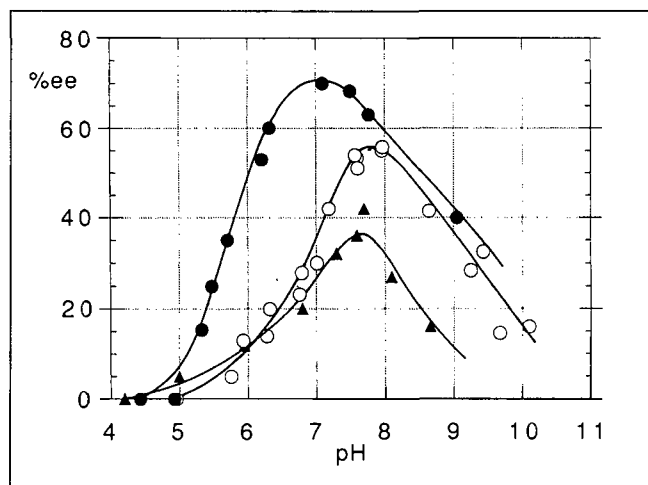


Fig. 1. Measured % ee of (R)-phenylalanine as a function of pH, formed between pyridoxamine and phenylpyruvate in the presence of [Cu((S,S)-HO-L)] (▲; reaction time 6 h), [Cu((S,S)-MeO-L)] (○), and [Cu((S,S)-BzO-L)] (●; reaction time 15 min). Conditions as given in the text and in the Exper. Part.



Introduction

Isomerization of Cu^{II} Schiff-base complexes formed by pyridoxamine and α -keto acids, yields pyridoxal and the corresponding α -amino acids. Chiral amino acids can be obtained under diastereoface-differentiating conditions which can be achieved either by implanting a chiral center in the Schiff base [3–9], or by employing a substrate-independent chiral ligand attached to Cu^{II}, see Scheme 1 [10][11].

In previous communications, we have reported [10][11] that the reaction using **I** as an auxiliary ligand shows quite high stereoselectivity, but the amount of the isolated amino acids was much smaller due to subsequent racemization of the isomerization product. We now present some results on the stereoselectivity of the isomerization of the Cu^{II} Schiff-base complex of pyridoxamine and phenylpyruvic acid in the presence of **II**, and **IIIa–c** as auxiliary ligands. The synthesis of the ligands, their Cu^{II} complex formation equilibria in solution, as well as the X-ray crystal structures of the Cu^{II} complexes with **II** and **IIIa–c** are discussed in previous [12][13] and forthcoming [14] publications.

Results

Fig. 1 shows the % ee of the isolated amino acid for the systems with **IIIa–c** as a function of pH. The stereoselectivity of the reaction generally increases from pH ≤ 4 and reaches a maximum at pH ≈ 7.5 before decreasing again.

Although the behavior of the three ligands seems very similar, an important difference exists. Whereas (R)-phenylalanine is configurationally stable in the presence of the ligand **IIIa**, complete racemization of the initially optically active amino acid is observed with **IIIb** and **IIIc**. The points reported in Fig. 1 for these two ligands are % ee values measured after 15 min reaction time at 25°, corresponding to an isomerization of 12 and 30%, respectively, which is sufficiently high to determine the enantiomeric ratio precisely.

The different behavior of **IIIa** and **IIIb** is shown in Fig. 2. Typical results of all the five ligands studied so far are given in the Table, together with some thermodynamic data of the corresponding Cu^{II} complexes.

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Discussion

A quantitative analysis of the system is difficult, because only few of the numerous equilibrium and rate constants which control the systems are known. On the other hand, the different behavior can be rationalized in a qualitative way by the four different pathways A–D (Scheme 2):

Pathway A: **1** → **2** (**9**) → **3** (**10**) → **11**

Pathway B: **1** → **4** → **5** → **11**

Pathway C: **1** → **6** → **7** → **5** → **11**

Pathway D: **1** → **6** → **7** → **8** → **11**

Pathways A and B lead to racemic products, whereas pathway C gives an optically active product, followed by racemization. A stable optically active product is obtained by pathway D (grey background in Scheme 2).

In basic solution pathway A is favored by both $[\text{CuL(OH)}]^+$ formation and stabilization of the free *Schiff* base by deprotonation of pyridoxamine. Pathway B, on the other hand, becomes relatively more important in acidic solution due to the different relative influence of protonation on the

formation of the different Cu^{II} complexes involved. The factors which control the relative importance of pathway C and D can be discussed on the basis of the data given in the Table. Pathway D seems clearly preferred for ligands showing high complex-formation constants. On the other hand, the stereoselectivity of the reaction seems to decrease as the stability of the complex with the optically active ligand increases. This could be due to a lower amount to the ketimine mixed ligand complex, the key intermediate for the formation of an optically active product, which, together with a slower reaction rate would then allow a relatively higher contribution of pathway A.

Finally, the question arises, whether the preferential formation of one enantiomer of phenylalanine can be understood on the basis of structural models of the reacting mixed ligand Cu^{II} complexes. The situation is schematically represented in Fig. 3 for the optically active triamines **II** and **III**.

The C_2 symmetry of these ligands allows only one geometrical arrangement of the tridentate *Schiff* base, which must adopt

a meridional coordination mode. In the ketimine form, the α -C-atom of the keto acid moiety has sp^2 geometry and the substituent carried by this C-atom lies in the coordination plane of the *Schiff* base ligand, whereas the six-membered ring is puckered, locating the pyridine moiety of the *Schiff* base outside of this plane. On isomerization, the substituent moves out of this plane, whereas the six-membered ring becomes almost coplanar.

As is easily recognized from Fig. 3, the formation of phenylalanine with (*R*)-configuration is favored when ligand **II** shows the (+)-(*R,R*)- and the ligands **IIIa–c** the (*S,S*)-configuration. One may argue that the ligands of type **III** can yield three different diastereoisomeric complexes according to the absolute configuration (*R*) or (*S*) of the coordinated N-atoms of the pyrrolidine rings. However, it can be seen from model considerations that the coordination of the tridentate *Schiff* base can only occur on the diastereoisomer represented in Fig. 3, in which the coordinated asymmetric N-atom shows (*S*)-configuration for the case of (*S,S*)-configuration of the ligands. In the other two diaster-

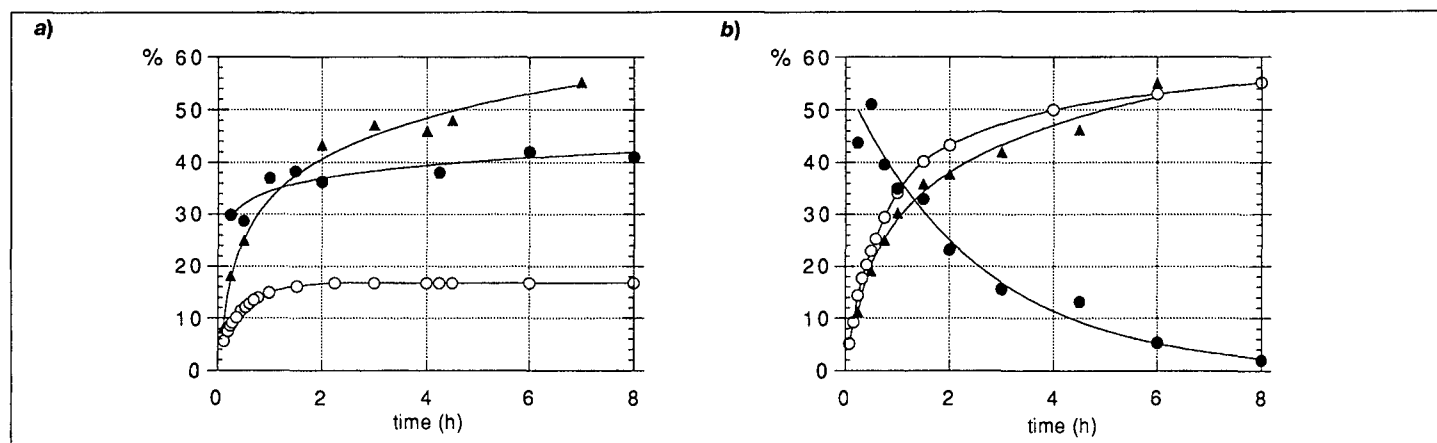


Fig. 2. Evolution in time of % ee of (*R*)-phenylalanine (●), % of Cu^{II} -aldimine complex measured by UV absorption at $\lambda = 386 \text{ nm}$ (○), and total amount of phenylalanine formed (▲): a) $[\text{Cu}((S,S)\text{-HO-L})]$, b) $[\text{Cu}((S,S)\text{-MeO-L})]$. Conditions as given in the Exper. Part.

Table. Enantioselective Formation of (*R*)-Phenylalanine by the Isomerization of Cu^{II} -Pyridoxylimino-Phenylpyruvate in the Presence of Various Tridentate Optically Active Ligands

Ligand	pH	Max. Abs. $\lambda = 386 \text{ nm}$	Selectivity % ee measured	% ee extrapolated ^{a)}	Racemization	Main pathway	$\log K^b)$	$\log k_{\text{OH}}^c)$	Ref.
(<i>R,R</i>)- I	5	weak	45 (<i>R</i>) ^{d)}	≈ 80 (<i>R</i>)	fast	C	10.5	7.7	[10]
(<i>R,R</i>)- II	5	Medium	0	—	—	B	16.8	8.5	[12][13]
	8	weak	24 (<i>R</i>) ^{e)}	—	—	D			
	12	weak	0	—	—	A			
(<i>S,S</i>)- IIIa	7.7	15% ^{h)}	42 (<i>R</i>) ^{f)}	—	—	D	13.1	8.0	this work
(<i>S,S</i>)- IIIb	7.9	$\approx 55\%$ ^{h)}	59 (<i>R</i>) ^{g)}	≈ 70 (<i>R</i>)	fast	C	12.2	8.6	this work
(<i>S,S</i>)- IIIc	7.1	$\approx 100\%$ ^{h)}	70 (<i>R</i>) ^{h)}	≈ 90 (<i>R</i>)	fast	C	11.7	8.7	this work

^{a)} Extrapolated to $t = 0$ for reactions followed by racemization. ^{b)} For the equilibrium $\text{CuL}/\text{Cu} \cdot \text{L}$. ^{c)} For the equilibrium $\text{CuL}(\text{H}_2\text{O})/\text{CuL}(\text{OH}) \cdot \text{H}$.

^{d)} Measured after a reaction time to attain maximum CD intensity at $\lambda = 386 \text{ nm}$. ^{e)} Observed after 90% conversion. ^{f)} Observed after 60% conversion.

^{g)} Observed after 15 min of reaction. ^{h)} Compared to the reaction without ligand.

oisomers, one or both of the CH_2OR substituents are placed in a position, giving strong steric interactions with any co-ordinated group situated in the apical positions of the coordination sphere of the mixed ligand Cu^{II} complex.

Experimental

1. *Apparatus.* Optical rotations: Perkin-Elmer 241 polarimeter. UV/VIS Spectra: Uvicon 820 spectrophotometer. HPLC Analyses: pump Perkin-Elmer series 10, detector Perkin-Elmer Tridet, integrator LCI-100.

2. *Products.* All the commercially available products were of anal. grade. The optically active ligands and the corresponding Cu^{II} complexes used in this work have been obtained according to [12] for **II** and [14] for **IIIa-c**.

(+)-1-(9-Fluorenyl)ethyl chloroformate was obtained according to [15], except for the optical resolution of 1-(9-fluorenyl)ethanol which was achieved using (*S*)-camphanyl chloride in place of *D*-camphor-10-sulfonate. The crude ester (yield 84%) was recrystallized 8 times in EtOH giving 22% of pure (+)-1-(9-fluorenyl)ethyl (*S*)-camphanate ester. The optical purity was checked by HPLC on a chiral stationary Pirkle's phase ((*R*)-dinitrobenzoylphenylglycine coupled to amino-propylsilica). M.p. 158°, $[\alpha]_{589} = +49$ ($c = 0.1$, EtOH).

1.2 g (30 mmol) of LiAlH_4 was added portionwise to a soln. of 1.0 g (2.56 mmol) of the (+)-1-(9-fluorenyl)ethyl (*S*)-camphanate ester in 50 ml of dried Et_2O and the suspension was stirred for 1 h at r.t. After addition of 2 ml of AcOEt and 2 ml of H_2O , the suspension was filtered and the solid well washed with CH_2Cl_2 . The org. solns. were combined, dried (MgSO_4), concentrated, and purified by chromatography (Al_2O_3 507C, 50×2 cm, petroleum ether/ CH_2Cl_2 40:60). The fractions containing (+)-1-(9-Fluorenyl)ethanol were combined and the solvent eliminated under vacuum. The crude product was recrystallized in ligroin giving 0.29 g (1.39 mmol; 54%), of fine white crystals. $[\alpha]_{589} = +30$ ($c = 0.1$, CH_2Cl_2).

3. *Reactions.* For reactions in the presence of ligand (*R,R*)-**I**, see [10].

3.1. *General.* All solns. were prepared in bidistilled H_2O except for reactions in the presence of ligand (*S,S*)-**IIIc**, where a 70:30 bidistilled H_2O /EtOH *p.a.* mixture was used, due to low solubility of this ligand and its complexes in water. Solns. were degassed, kept under N_2 , and thermostated at 25° during the reaction. The ionic strength was fixed at 0.1 by the buffer solns. used in the different pH domains (acetate, citrate, borate, or phosphate).

3.2. *Isomerization in the Presence of (R,R)-II.* To 1 ml (0.02 mmol) of a 0.02M soln. of $[\text{Cu}(\text{R,R-II})](\text{ClO}_4)_2$ [13] was added 1 ml (0.02 mmol) of a 0.02M soln. of pyridoxamine HCl (Merck *p.a.*), 3 ml (0.3 mmol) of a 0.1M soln. of sodium phenylpyruvate (Fluka *p.a.*) and 2 ml of a 0.5M buffer soln. The mixture was diluted to 10 ml.

3.3. *Isomerization in the Presence of (S,S)-IIIa, (S,S)-IIIb, and (S,S)-IIIc.* Crystallized $[\text{Cu}(\text{L})\text{Cl}](\text{ClO}_4)_2$ obtained as described in [14] (0.1 mmol for **L** = (*S,S*)-**IIIa** and (*S,S*)-**IIIb**, 0.022 mmol for (*S,S*)-**IIIc**) was dissolved in 30 ml of the corresponding solvent (see 3.1). 5 ml of the 1M

Scheme 2

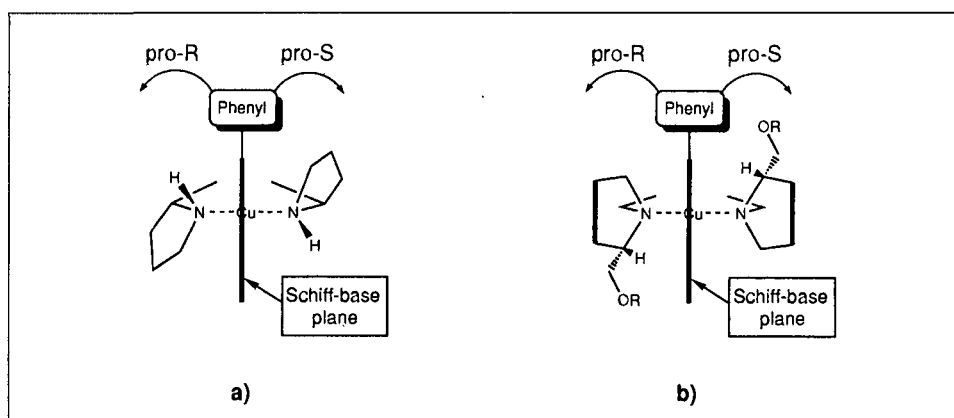
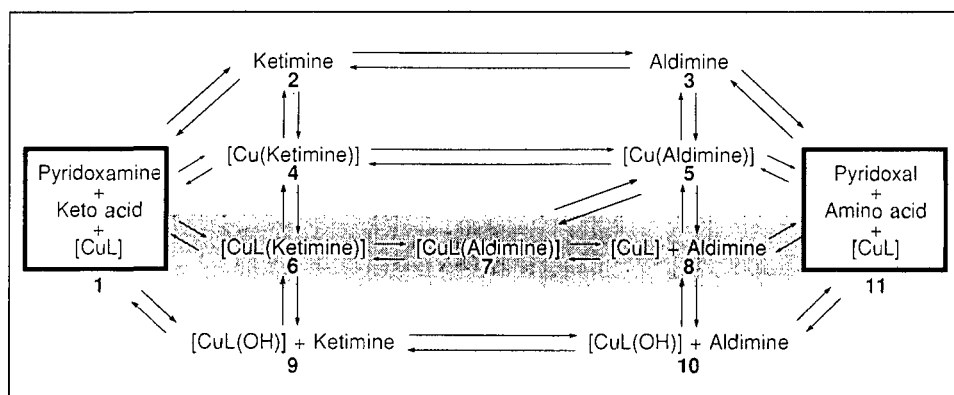


Fig. 3. Schematic representation of possible stereochemical pathways in the evolution of the Cu^{II} /ligand/ketimine intermediate complexes: a) ligand = (*R,R*)-**II**, b) ligands = (*S,S*)-**IIIa-c**.

buffer soln. and 5 ml of a soln. containing 1 equiv. of pyridoxamine HCl were added. If necessary, the pH was adjusted to the desired value with dil. HCl or NaOH. The reaction was started by addition of 5 ml of a soln. containing 7.5 equiv. of sodium phenylpyruvate and adjusting the total volume to 50 ml.

4. *Analyses.* 4.1. *Isolation and Derivatization of Amino Acids.* At various reaction times aliquots containing ~0.005 mmol of the amino acids were withdrawn from the soln. The pH was fixed at 2 with dil. HCl and 0.003 mmol of (*R*)-alanine was added as an internal standard. The soln. was introduced onto a small chelating ion-exchange column (*Acryl-IDA*, Na^+ , 4×1.5 cm) and eluted with H_2O . The $[\text{CuL}]$ complex is retained on the column while the amino acids are eluted. The eluent was neutralized, concentrated to ~10 ml, and the amino acids derivatized with (+)-1-(9-fluorenyl)ethyl chloroformate, as described in [15].

4.2. *HPLC Measurements.* A 5- μl sample of the soln. of derivatized amino acids (see 4.1) was injected onto a column (*Nucleosil 100-5C₈* reversed phase, 250×4 mm), equipped with a precolumn (*Nucleosil 120-5C₁₈* reversed phase, 30×4 mm). The mobile phase consisted of THF (55%) and 0.1M AcOH buffer, pH 4.75 (45%); flow rate was 0.6 ml/min. Typical retention times were 6.1 min for the (*R*)-alanine derivative, 8.3 min for the (*R*)-phenylalanine derivative, 9.5 min for the (*S*)-phenylalanine derivative, and 11.5 min for the hydrolyzed (+)-1-(9-fluorenyl)ethyl chloroformate.

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156. Stereoselectivity in Reactions of Metal Complexes

Part XVII¹⁾

Synthesis of Three New Optically Active Triamines: 2,6-Bis{[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}pyridine, 2,6-Bis{[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}pyridine, and 2,6-Bis{[(2*S*)-2-[(benzyloxy)methyl]pyrrolidin-1-yl]methyl}pyridine. X-Ray Structure and Equilibrium Behaviour of Their Copper(II) Complexes

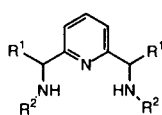
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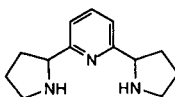
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The three new optically active triamines derived from 2,6-bis(aminomethyl)pyridine, *i.e.* 2,6-bis{[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}pyridine (**3a**), 2,6-bis{[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}pyridine (**3b**), and 2,6-bis{[(2*S*)-2-[(benzyloxy)methyl]pyrrolidin-1-yl]methyl}pyridine (**3c**), were synthesized. The equilibrium behaviour in solution and Cu^{II} complex formation were studied by acidimetric titration and by UV/VIS and CD measurements. It was found that in aqueous solution, **3a** can coordinate one of the CH₂OH groups to Cu^{II} upon deprotonation. X-Ray crystal structures were determined for the complexes [Cu(**3a**)Cl]ClO₄·H₂O, [Cu(**3b**)Cl]ClO₄, and [Cu(**3c**)Cl]ClO₄. In the solid state, coordination of both the OH and the alkoxy groups was observed, and the three ligands are pentacoordinated.

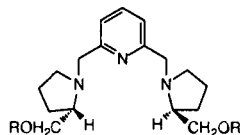
Introduction. – Optically active *C*₂-symmetric triamines were used as auxiliary ligands in enantioselective reactions involving copper(II) *Schiff*-base complexes [2–5]. Despite quite important asymmetric inductions observed with ligands **1** or **2**, the influence of the substituents at the chiral centers of compounds with framework **1** is not easy to understand due to rotational freedom of the chiral groups in the reacting mixed ligand complex. The ligands of type **3** were selected for two reasons: *i*) the large possibilities of variation of the substituents without changing the basic structure of the ligand and *ii*) the introduction of O-carrying side chains which allow supplementary interactions with a coordination center.



1a R¹ = R² = Me
b R¹ = H, R² = Ph(Me)CH



2



3a R = H
b R = Me
c R = PhCH₂

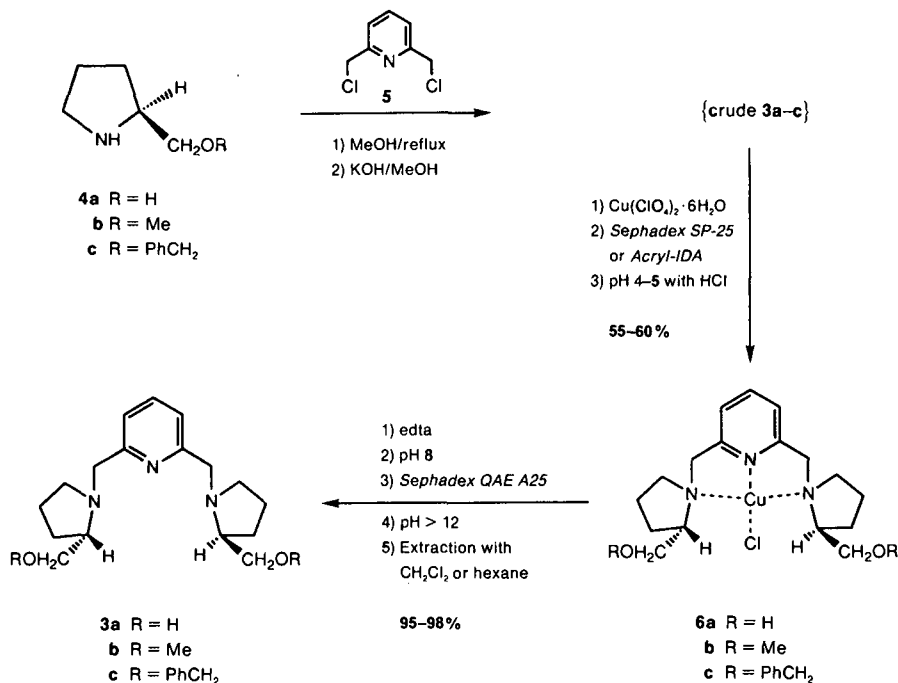
¹⁾ Part XVI, see [1].

²⁾ Part of the Ph. D. Thesis of Th. C.

In the present paper, we report the synthesis of **3a–c**, the X-ray crystal structures of their Cu^{II} complexes, and the equilibrium behaviour of these complexes in solution. The use of the ligands as auxiliary ligands in the enantioselective formation of phenylalanine by the isomerization of the mixed ligand *Schiff*-base complex from pyridoxamine and phenylpyruvic acid is reported in a separate communication [6].

Results and Discussion. – 1. *Synthesis.* The ligands **3a–c** were synthesized by reacting 2,6-bis(chloromethyl)pyridine (**5**) with (*S*)-prolinol (**4a**), (*S*)-2-(methoxymethyl)pyrrolidine (**4b**), or (*S*)-2-[(benzyloxy)methyl]pyrrolidine (**4c**), respectively (*Scheme 1*). The

Scheme 1



ligands were isolated and purified as their Cu^{II} complexes **6a–c** by ion-exchange chromatography. The pure free (*S,S*)-ligands **3a–c** were then obtained from the crystallized complexes by adding a slight excess of Na₂H₂edta followed by ion-exchange chromatography.

2. *Structures.* X-Ray crystal structures of the Cu^{II} complexes **6a–c** (obtained from the purified ligands **3a–c**), containing a coordinated Cl[–] ion *trans* to the pyridine N-atom, are shown in *Fig. 1*, and selected bond lengths and bond angles are given in *Table 1*.

To illustrate several common characteristic features, different views of the three compounds are represented: [Cu(**3a**)Cl]ClO₄ · H₂O is shown in the plane containing the pyridine ring and the N(1)–Cu–Cl axis. [Cu(**3b**)Cl]ClO₄ and the two independent

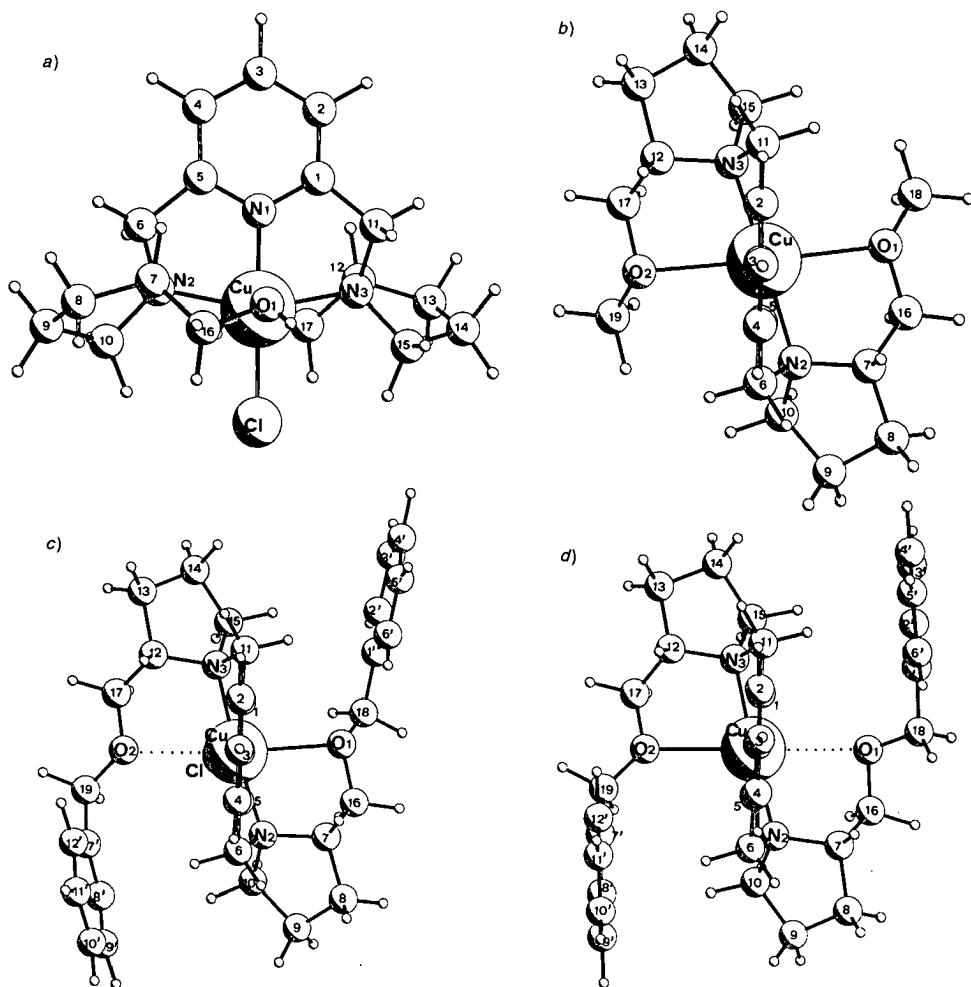


Fig. 1. PLUTO [15] plots of a) $[\text{Cu}(\mathbf{3a})\text{Cl}]\text{ClO}_4 \cdot \text{H}_2\text{O}$, b) $[\text{Cu}(\mathbf{3b})\text{Cl}]\text{ClO}_4$, c) $[\text{Cu}(\mathbf{3c})\text{Cl}]\text{ClO}_4$ (molecule A), and d) $[\text{Cu}(\mathbf{3c})\text{Cl}]\text{ClO}_4$ (molecule B). Arbitrary numbering scheme.

molecules of $[\text{Cu}(\mathbf{3c})\text{Cl}]\text{ClO}_4$, on the other hand, are drawn so as to highlight the coordination of the MeO and the PhCH_2O group, respectively. The two independent molecules A and B per asymmetric unit in the crystal of $[\text{Cu}(\mathbf{3c})\text{Cl}]\text{ClO}_4$ (Figs. 1c and 1d) differ by the orientation of the PhCH_2O group at atom O(1). Torsion angle $\text{C}(7)–\text{C}(16)–\text{O}(1)–\text{C}(18)$ is 106.6° in molecule B and -174.6° in molecule A. The latter value is similar to that found in $[\text{Cu}(\mathbf{3b})\text{Cl}]\text{ClO}_4$ for the torsion angles involving atoms O(1) and O(2) (176.4 and 175.2° , resp.). In $[\text{Cu}(\mathbf{3c})\text{Cl}]\text{ClO}_4$, torsion angle $\text{C}(12)–\text{C}(17)–\text{O}(2)–\text{C}(19)$ is 173.6° in molecule A and 160.6° in molecule B.

For stability reasons, the chloro complexes were preferred to the aquo complexes for the structural determinations, because they crystallized spontaneously from aqueous

Table 1. Selected Bond Lengths [Å] and Angles [°] for Cu^{II} Complexes **6a–c** with Ligands **3a–c**

	[Cu(3a)Cl]ClO ₄ ·H ₂ O	[Cu(3b)Cl]ClO ₄	[Cu(3c)Cl]ClO ₄	
			Molecule A	Molecule B
Cu–Cl	2.2205(18) ^{a)}	2.2248(14)	2.204(3)	2.196(4)
Cu–N(1)	1.939(5)	1.930(4)	1.938(9)	1.928(10)
Cu–N(2)	2.130(6)	2.112(5)	2.107(10)	2.102(11)
Cu–N(3)	2.106(6)	2.099(5)	2.112(10)	2.142(11)
Cu–O(1)	2.453(6)	2.466(4)	2.563(8)	2.685(11)
Cu–O(2)	2.482(6)	2.522(5)	2.664(8)	2.532(11)
Cl(1)–Cu–N(1)	178.53(17)	179.00(14)	175.0(3)	177.7(4)
Cl(1)–Cu–N(2)	100.48(17)	100.43(13)	101.1(3)	99.7(3)
Cl(1)–Cu–N(3)	100.00(18)	100.02(14)	100.2(3)	99.2(3)
Cl(1)–Cu–O(1)	93.36(20)	92.94(14)	88.36(20)	88.4(3)
Cl(1)–Cu–O(2)	93.20(17)	89.70(12)	87.45(21)	93.3(3)
N(1)–Cu–N(2)	80.02(23)	79.44(18)	78.7(4)	81.7(4)
N(1)–Cu–N(3)	79.44(23)	80.11(19)	80.3(4)	79.4(4)
N(1)–Cu–O(1)	88.10(25)	86.07(19)	96.5(3)	90.2(4)
N(1)–Cu–O(2)	85.36(22)	91.30(17)	87.8(3)	88.1(4)
N(2)–Cu–N(3)	159.39(24)	159.55(18)	158.6(4)	161.1(4)
N(2)–Cu–O(1)	77.69(22)	78.81(20)	78.4(3)	76.8(4)
N(2)–Cu–O(2)	97.89(22)	102.48(19)	107.2(3)	102.6(4)
N(3)–Cu–O(1)	103.38(21)	100.08(21)	100.2(3)	102.3(3)
N(3)–Cu–O(2)	78.66(20)	77.67(19)	75.7(3)	77.6(4)
O(1)–Cu–O(2)	172.68(24)	176.81(17)	173.5(3)	178.3(4)

^{a)} The uncertainty on the last digit is given within parentheses.

solutions or H₂O/EtOH mixtures containing Cl[–] ions. The Cl[–] ion is retained in the coordination sphere when the compounds are recrystallized from the pure solvents. The most salient feature of the molecular arrangement of the ligands is the pentacoordination observed for all three compounds, with the O-atom of the OH or alkyloxy groups in the apical position of the distorted octahedron. This coordination gives (*R*)-chirality to the two asymmetric N-atoms and *Λ*-configuration to the complex in the cases of the ligands with (*S,S*)-configuration (see Fig. 1). The Cu–O bonds are slightly longer than in comparable compounds. *E.g.*, the standard average of the longest Cu–O (ROH, R = C(sp³)) bond is 2.384 Å [7], compared to 2.466 and 2.522 Å in [Cu(**3b**)Cl]ClO₄ and 2.532–2.685 Å in molecules A and B of [Cu(**3c**)Cl]ClO₄ (see Table 1). The two Cu–O bond length differ slightly, and this difference increases in the order Cu-**3a** < Cu-**3b** < Cu-**3c**, as both bonds become longer. The N(1)–Cu–O(1 or 2) bond angles increase in the same order, that is Cu-**3a** < Cu-**3b** < Cu-**3c** (molecule A). Molecule B of Cu-**3c** is an exception, with the largest difference between the Cu–O bond lengths, 0.153 Å (0.101 Å in molecule A), but the smallest difference in the N(1)–Cu–O(1 or 2) bond angles, 2.1° (8.7° in molecule A). In all three complexes, the pyridine ring is twisted with respect to the plane through atoms N(2), Cu, and N(3) by an average value of 19°. The pyrrolidine rings of all three compounds have envelope conformations with atoms C(10) and C(15) being displaced by more than 0.5 Å from the planes defined by the remaining four atoms in the respective rings. The chelate rings involving atoms N(2) and N(3) also exist in envelope conformations in all three complexes (supplementary data). There are no short (< 3.2 Å) inter-

molecular contacts between non-H-atoms in the crystals of any of the three compounds. The geometry mentioned above appears to be dictated by the configuration at atoms N(2) and N(3).

3. *Equilibrium Measurements.* The acid dissociation of the three ligands as well as the complex-formation constants with Cu^{II} were determined by acidimetric titrations (*Table 2*). The complex-formation equilibria were also determined by spectrophotometric and spectropolarimetric measurements, and the values obtained from potentiometric and from the spectroscopic methods are in sufficiently good agreement (see *Table 2*).

Table 2. *Equilibrium Constants (log K) for the System Cu^{II}/Ligand L (L = 1a, b, 2, and 3a–c).*
T = 25°; $\mu = 0.1$ (NaNO₃).

Equilibrium	L = 1a ^{a)}	L = 1b ^{b)}	L = 2 ^{c)}	L = 3a ^{d)} e)	L = 3b ^{d)} e)	L = 3c ^{d)} e)f)
H ₂ L/H · HL	9.00	7.49	9.39	7.68(1)	7.54(1)	6.99(1)
HL/H · L	9.80	8.57	10.14	8.49(3)	8.37(2)	8.33(2)
[Cu ^{II}]/Cu ^{II} · L	14.13	10.50	16.80	13.13(5)	12.15(10)	11.69(7)
				13.1(1) ^{g)}	12.3(1) ^{g)}	11.8(1) ^{g)}
[Cu ^{II} L(H ₂ O)]/H · [Cu ^{II} L(OH)]	8.50	7.7	8.49	7.94(2) ^{h)}	8.51(2)	8.69(3)
[Cu ^{II} L(OH)]/H · [Cu ^{II} LH ₂ (OH)]	–	–	–	10.85(4) ^{h)}	–	–

a) From [4].

b) From [3].

c) From [8].

d) For potentiometric measurements, mean values from at least 4 titrations.

e) The uncertainty on the last digit is given in parentheses.

f) Determined in H₂O/EtOH 62.5:37.5.

g) Mean values from spectrophotometric and spectropolarimetric measurements.

h) For the exact signification of the equilibrium constant, see text.

For solubility reasons, the measurements with 3c were made in H₂O/EtOH mixtures, thus the results given in *Table 2* cannot be directly compared to those given for 3a and 3b. Only the data obtained in aqueous solution will, therefore, be considered in the following discussion. From the values in *Table 2* it is seen that the protonation constants involving the two tertiary N-atoms of 3a and 3b are very similar and comparable to those of 1b, a ligand containing two secondary N-atoms, the substituents of which apparently decrease the electron density and, therefore, the basicity of the N-atoms. On the other hand, the secondary N-atoms of the ligands 1a and 2 show much higher proton affinity, which difference can, at least partially, explain the large variation of more than six orders of magnitude in the formation constants of the corresponding Cu^{II} complexes. The higher stability of the Cu^{II} complex with 3a compared to 3b is difficult to explain on the sole basis of the basicity difference of the coordination atoms. The presence of the CH₂OH groups can enhance the stability either by coordination or by intramolecular H-bond formation. A similar stability increase due to the presence of hydroxyalkyl groups was reported for other systems [8].

The acid dissociation constants of the Cu^{II} complexes need some more detailed discussion. From the values given in *Table 2* it is seen that the acid dissociation constants of the Cu^{II} complexes with 1a, 2, and 3b are almost identical. To permit a comparison with the behaviour of other Cu^{II} complexes, formation and acid-dissociation constants for some similar systems are collected in *Table 3*. The coordinated H₂O molecule in the

Table 3. Formation and Acid Dissociation Constants of Cu^{II} Complexes with Some Selected Linear Triamine Ligands

Ligand	$\log K^{\text{a}}$	$\log K_{\text{a}}^{\text{b}}$	Ref.
2,6-bis(aminomethyl)pyridine	15.7	8.93	[9]
1,4,7-triazaheptane	16.1	9.4	[10]
5-methyl-2,5,8-triazanonane	13.17	8.57	[10]
2,5,8-trimethyl-2,5,8-triazanonane	12.16	8.65	[10]
2,2'-(iminobis(methylene))bis(pyridine)	14.4	7.94	[11]

^a) $K = [\text{Cu}^{\text{II}}\text{L}]/[\text{Cu}^{\text{II}} \cdot \text{L}]$. ^b) $K_{\text{a}} = [\text{Cu}^{\text{II}}\text{L}(\text{H}_2\text{O})]/\text{H} \cdot [\text{Cu}^{\text{II}}\text{L}(\text{OH})]$.

complex with 2,6-bis(aminomethyl)pyridine, the ligand with unsubstituted terminal amino groups, is slightly less acid, but there seems to be no significant difference between secondary and tertiary terminal amines, as shown by the comparison of the complexes with **1a**, **2**, and **3b**, respectively. The same observation can be made, when the aliphatic ligands 1,4,7-triazaheptane, 5-methyl-2,5,8-triazanonane, and 2,5,8-trimethyl-2,5,8-triazanonane are compared.

An easier H^+ dissociation from the coordinated H_2O molecule is only observed for ligands containing more than one electron-withdrawing group, e.g. 2,2'-(iminobis(methylene))bis(pyridine) and **1b**. The significantly higher acidity of the Cu^{II} aqua complex with **3a** with an apparent acid dissociation constant of $1.15 \cdot 10^{-8}$ can, therefore, hardly be explained assuming higher acidity of the coordinated H_2O molecule. More reasonably, the higher acidity should be attributed to another chemical reaction. The most likely would be the deprotonation of one of the CH_2OH groups upon coordination, or of the dissociation of such a group already coordinated. The existence of such a 'methoxy ring-closed' species is strongly supported by spectroscopic measurements. When the VIS spectrum of $[\text{Cu}^{\text{II}}(\text{3b})]$ (CH_2OMe -substituted ligand) is measured as a function of pH (Fig. 2b), an increase of the absorption is observed corresponding to the complex formation which is almost complete at pH 6. At $\text{pH} > 7$, the intensity of the absorption decreases again, and the absorption maximum is slightly shifted to longer

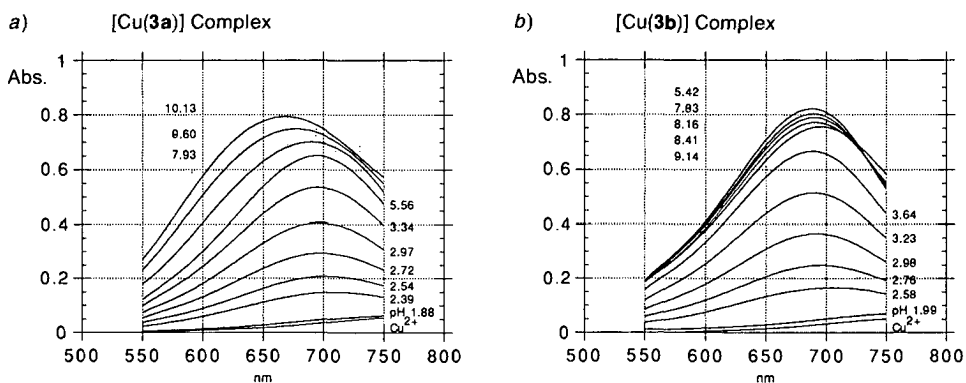


Fig. 2. VIS-Absorption spectra of a) $[\text{Cu}(\text{3a})\text{H}_2\text{O}]^{2+}$ and b) $[\text{Cu}(\text{3b})\text{H}_2\text{O}]^{2+}$ at different pH. $[\text{CuL}]_{\text{tot}} = 5.0 \cdot 10^{-3} \text{ M}$, $T = 25^\circ$, $\mu = 0.1$ (NaNO_3).

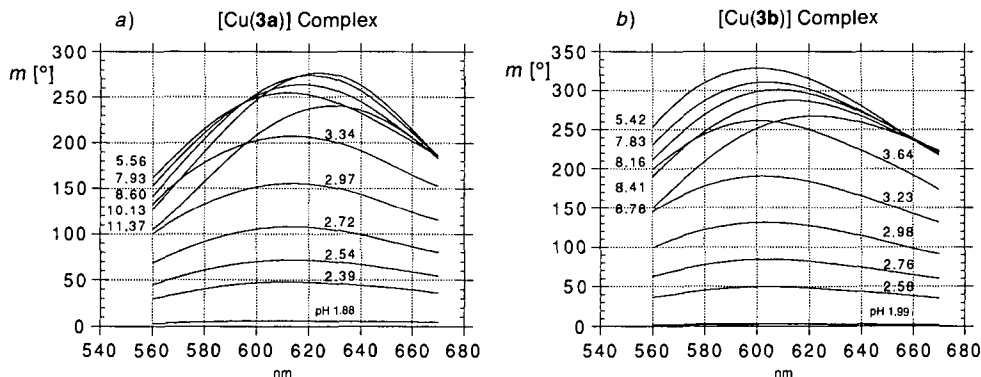


Fig. 3. CD Spectra of a) $[\text{Cu}(\mathbf{3a})\text{H}_2\text{O}]^{2+}$ and b) $[\text{Cu}(\mathbf{3b})\text{H}_2\text{O}]^{2+}$ at different pH. Conditions as in Fig. 2.

wavelength. The isosbestic point at 730 nm indicates the equilibrium between two species only. The behaviour of $[\text{Cu}^{\text{II}}(\mathbf{3a})]$ (CH_2OH -substituted ligand) is very similar in acidic solution but differs significantly at $\text{pH} > 7$ (Fig. 2a). The absorption intensity continues to increase and the absorption band shows a hypsochromic shift. No isosbestic point is observed. The situation seems even clearer when the CD spectra of the same systems are considered (Fig. 3). Whereas for $[\text{Cu}^{\text{II}}(\mathbf{3b})]$, a simple two-component equilibrium with a single isodichroic point at 660 nm is observed (Fig. 3b), $[\text{Cu}^{\text{II}}(\mathbf{3a})]$ shows a three-step reaction (Fig. 3a). After the complex formation, a first reaction is observed in the pH interval of ca. 6–9 in which the CD intensity continues to increase and an isodichroic point is observed at 595 nm. When the pH of the solution continues to increase, further spectral changes occur which are very similar to those observed for $[\text{Cu}^{\text{II}}(\mathbf{3b})]$ at slightly lower pH values: decrease of the intensity and appearance of an isodichroic point at ca. 660–670 nm.

The measured equilibrium constants for the deprotonation of $[\text{Cu}(\mathbf{3b})(\text{H}_2\text{O})]^{2+}$ and $[\text{Cu}(\mathbf{3a})(\text{H}_2\text{O})]^{2+}$ are different by only 0.57 log units (see Table 2), and it can, therefore, be assumed that $[\text{Cu}(\mathbf{3a})(\text{H}_2\text{O})]^{2+}$ will be deprotonated simultaneously, either at the coordinated H_2O molecule or at the CH_2OH group, yielding an open (C) and a closed (B) deprotonated form in a pH-independent equilibrium (see Scheme 2). The ratio of the two forms is given by the ratio of the individual acid-dissociation constants $K_{\text{a}(\text{C})}$ and $K_{\text{a}(\text{B})}$ for the open and the closed forms, respectively (Eqn. 1).

$$[\text{C}]/[\text{B}] = [\text{Cu}(\text{HO} - \text{L}')(\text{OH})]^+ / [\text{Cu}(\text{O} - \text{L}')(\text{H}_2\text{O})]^+ = K_{\text{a}(\text{C})} / K_{\text{a}(\text{B})} \quad (1)$$

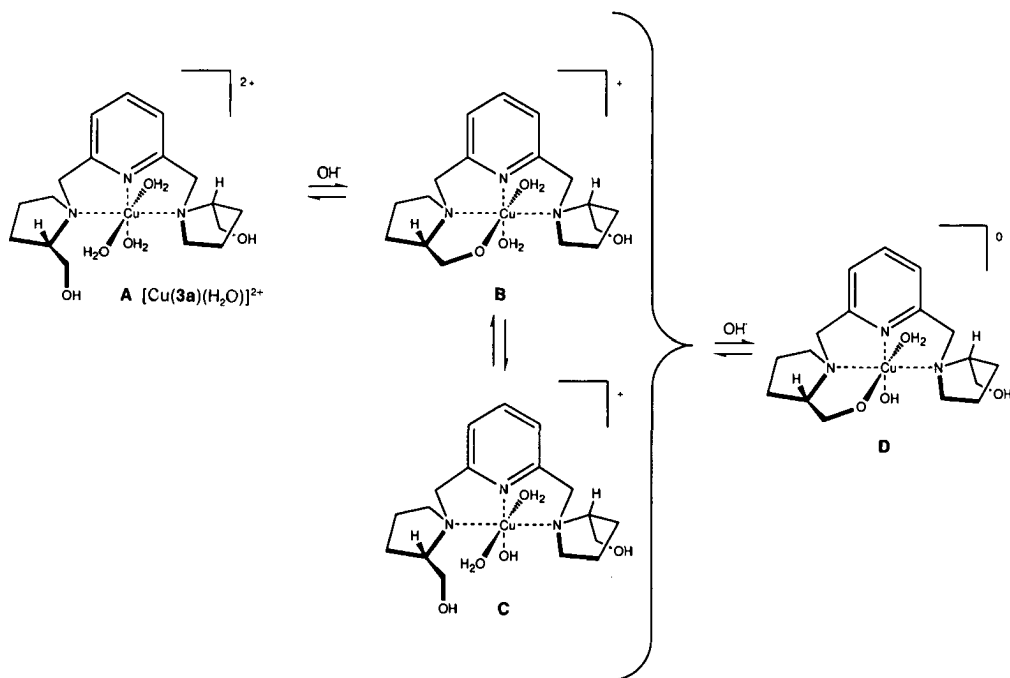
The apparent dissociation constant given in Table 2 which is obtained from the titration curve represents the sum of the two individual constants for the two different dissociation modes (Eqn. 2).

$$K_{\text{app}} = [\text{H}^+] \cdot a / (1 - a) = K_{\text{a}(\text{C})} + K_{\text{a}(\text{B})} \quad (2)$$

(a = equivalents of added base)

The individual dissociation constants are not known and cannot be determined directly. On the other hand, considering the values given in Table 2, one would not expect

Scheme 2



the acid dissociation constants of the coordinated H_2O molecule in $[\text{Cu}(\mathbf{3a})(\text{H}_2\text{O})]^{2+}$ and $[\text{Cu}(\mathbf{3b})(\text{H}_2\text{O})]^{2+}$ to be significantly different. Assuming an identical value for these two complexes, a calculated value $-\log K_{\text{a(B)}} = 8.08$ is then obtained for the acid dissociation constant of the closed form **B**, corresponding to an approximate ratio of 7:3 for the pH-independent equilibrium between the closed and the open forms **B** and **C**, respectively.

The final question concerns the configuration of the deprotonated forms for which different diastereoisomers can exist. For electronic reasons, bonding in the tetragonal plane is much stronger than in the apical positions, and the reacting H_2O molecule will be the one located in the tetragonal plane, *trans* to the pyridine moiety of the ligand. On the other hand, the coordination of the deprotonated OH group will be more favourable in the apical position for evident stereochemical reasons. This hypothesis is supported by the observation that a second H^+ can be dissociated from the complex **B** ($= [\text{Cu}(\text{O} - \text{L}')(\text{H}_2\text{O})]^{2+}$; $-\log K = 10.85$) to give a neutral species **D** (see Scheme 2) but not from the complex $[\text{Cu}(\mathbf{3b})(\text{OH})]^+$ ($= [\text{Cu}(\text{MeO} - \text{L}')(\text{OH})]^+$). In the former case, the first H^+ dissociates mainly from the OH group coordinated in the apical position allowing a second H^+ dissociation from the H_2O molecule coordinated in the tetragonal plane ($\rightarrow \text{D}$).

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Experimental Part

1. *General.* Optical rotations: *Perkin-Elmer-M-240* polarimeter. UV/VIS Spectra: *Uvikon 820*; $\lambda_{\max}(\epsilon)$ in nm. CD Spectra: *Jasco J-500-C*; $\lambda(\Delta\epsilon)$ in nm. $^1\text{H-NMR}$ Spectra: *Bruker AMX 400*. Mass spectra: *Normag R-30-10*. X-Ray diffractometer: *Siemens-Stoe AED2*.

2. *Syntheses.* 2.1. (*S*)-2-[(*Benzoyloxy*)methyl]pyrrolidine (**4c**) was synthesized in analogy to [12] using benzyl bromide (26.9 g, 0.157 mol), (*S*)-1-formylprolinol [12] (12.1 g, 0.105 mol), and a 80 % dispersion of NaH (3.5 g, *ca.* 0.12 mol). Omitting distillation, the crude (*S*)-2-[(*benzyloxy*)methyl]-1-formylpyrrolidine was *N*-deprotected in refluxing 10 % KOH/H₂O soln. Distillation under high vacuum gave 17.2 g (59 %) of **4c**. B.p. 99–100°/0.07 Torr. $n_D^{20} = 1.528$. $[\alpha]_{589} = -0.6$, $[\alpha]_{365} = -11.4$ ($c = 2$, benzene), $\alpha_{589} = -0.66$ (neat, 1-cm cell). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.41 (*m*, 1 H); 1.60–1.86 (*m*, 3 H); 2.17 (*s*, 1 H); 2.85 (*m*, 1 H); 2.96 (*m*, 1 H); 3.26–3.52 (*m*, 3 H); 4.53 (*t*, 2 H); 7.25–7.36 (*m*, 5 H). MS: 192 ($[M + 1]^+$).

2.2. {2,6-Bis[[(2*S*)-2-(*hydroxymethyl*)pyrrolidin-1-yl]methyl]pyridine}chlorocopper(II) Perchlorate (**6**). A soln. of 2,6-bis(chloromethyl)pyridine (**5**; 6.96 g, 0.0395 mol) in freshly distilled MeOH (100 ml) was added dropwise to a soln. of (*S*)-prolinol (**4a**; 10.0 g, 0.0989 mol) in MeOH (150 ml). The mixture was heated under reflux and kept weakly alkaline (phenolphthalein) using a 10 % KOH/MeOH soln. When the pink colour persisted, the mixture was cooled. To complete the reaction, more **5** (1.39 g, 0.0079 mol) in MeOH (20 ml) was added dropwise and the mixture treated as above, and then evaporated. As ligand **3a** could not readily be isolated, the residue was dissolved in 1N HCl, a soln. of $\text{CuClO}_4 \cdot 6 \text{H}_2\text{O}$ (26.3 g, 0.0711 mol) in H₂O (100 ml) added (→dark green), the pH adjusted to 6–7 with dil. NaOH soln., and the mixture filtered to remove org. residues. The filtrate was introduced onto an ion-exchange column (*Sephadex SP-25*, Na^+) which was well washed with H₂O and then eluted with 2 % $\text{NaClO}_4/\text{H}_2\text{O}$ soln. (alternatively, **6a** was purified using an ion-exchange chelating phase (*Acryl-IDA*, Na^+) and a 0.01N $\text{Ca}(\text{ClO}_4)_2$ for elution). The deep blue fraction was collected and concentrated, the pH adjusted to 4–5 with dil. HCl soln., and the mixture left in the refrigerator: deep blue crystals. On successive concentrations, 13.1 g (55 %) of **6a** were obtained. $[\alpha]_{589} = -545$, $[\alpha]_{546} = -840$, $[\alpha]_{365} = -1520$ ($c = 0.03$, H₂O, pH 5.7). VIS (pH 5.6): 692 (138). CD (pH 5.6): 616 (+1.56). Anal. calc. for $(\text{C}_{17}\text{H}_{27}\text{ClCuN}_3\text{O}_2)\text{ClO}_4$ (503): C 40.6, H 5.4, N 8.3, Cl 14.1, C/N 4.86; found: C 40.2, H 5.5, N 8.1, Cl 13.1, C/N 4.94.

2.3. 2,6-Bis[[(2*S*)-2-(*hydroxymethyl*)pyrrolidin-1-yl]methyl]pyridine (**3a**). To a soln. of **6a** (0.904 g, 1.80 mmol) in 30 ml of H₂O 1.2 equiv. of Na₂H₂edta (2.16 mmol) were added. The pH was adjusted to 8 with a dil. NaOH soln. and the mixture introduced onto an ion-exchange column (*Sephadex QAE A25*, Cl^-); $[\text{Cu}(\text{edta})]^{2-}$, ClO_4^- , and $\text{H}_2\text{edta}^{2-}$ in excess were fixed on the column, while **3a** passed through. The column was washed with H₂O until the eluent showed no further optical activity. The soln. was concentrated, made strongly alkaline by adding 2N NaOH, and extracted with 3 portions of CH_2Cl_2 (30 ml) and the extract dried (MgSO_4) and evaporated: 0.522 g (95 %) of **3a**. Pale yellow crystalline solid. M.p. 94°. $[\alpha]_{589}^{25} = -32.8$, $[\alpha]_{365}^{25} = -112$ ($c = 0.5$, H₂O, pH 1.8). UV: 262 (3630), 206 (6700). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.74 (*m*, 6 H); 1.89 (*m*, 2 H); 2.45 (*q*, 2 H); 2.81 (*m*, 2 H); 3.04 (*m*, 2 H); 3.46 (*q*, 2 H); 3.64 (*q*, 2 H); 3.88 (*q*, 2 H); 4.6–5.8 (*br.*, 2 H); 7.13 (*d*, 2 H); 7.61 (*t*, 1 H). MS: 306 ($[M + 1]^+$). Anal. calc. for $\text{C}_{17}\text{H}_{27}\text{N}_3\text{O}_2$ (305): C 66.9, H 8.85, N 13.8, C/N 4.86; found: C 66.9, H 8.83, N 13.6, C/N 4.92.

2.4. {2,6-Bis[[(2*S*)-2-(*methoxymethyl*)pyrrolidin-1-yl]methyl]pyridine}chlorocopper(II) Perchlorate (**6b**) was synthesized as described in 2.2 using **5** (5.10 g, 0.0290 mol) and (*S*)-2-(*methoxymethyl*)pyrrolidine (**4b**; 6.70 g, 0.0583 mol). By successive concentration, 8.77 g (57 %) of **6b** were obtained. $[\alpha]_{589} = -450$, $[\alpha]_{546} = -910$, $[\alpha]_{365} = -1745$ ($c = 0.03$, H₂O, pH 5.7). VIS (pH 5.6): 686 (151). CD (pH 5.6): 608 (+1.67). Anal. calc. for $(\text{C}_{19}\text{H}_{31}\text{ClCuN}_3\text{O}_2)\text{ClO}_4$ (531): C 42.9, H 5.8, N 7.9, Cl 13.3, C/N 5.43; found: C 43.7, H 5.9, N 8.0, Cl 12.7, C/N 5.47.

2.5. 2,6-Bis[[(2*S*)-2-(*methoxymethyl*)pyrrolidin-1-yl]methyl]pyridine (**3b**) was isolated as described in 2.3 using 1.0 g (1.88 mmol) of **6b**: 0.614 g (98 %) of **3b**. Pale yellow oil. $[\alpha]_{589}^{25} = -14.4$, $[\alpha]_{365}^{25} = -49.9$ ($c = 0.5$, H₂O, pH 1.8). UV: 262 (3700), 206 (6700). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.71 (*m*, 6 H); 1.93 (*m*, 2 H); 2.34 (*q*, 2 H); 2.83 (*m*, 2 H); 3.01 (*m*, 2 H); 3.30 (*q*, 2 H); 3.32 (*s*, 6 H); 3.40 (*q*, 2 H); 3.90 (*q*, 4 H); 7.31 (*d*, 2 H); 7.60 (*t*, 1 H). MS: 334 ($[M + 1]^+$).

2.6. {2,6-Bis[[(2*S*)-2-(*benzyloxy*)methyl]pyrrolidin-1-yl]methyl]pyridine}chlorocopper(II) Perchlorate (**6c**) was prepared as described in 2.2 using **5** (5.51 g, 0.0314 mol) and (*S*)-2-[(*benzyloxy*)methyl]pyrrolidine (**4c**; 12.0 g, 0.063 mol). Because of its low solubility, **6c** was prepared, purified, and crystallized using H₂O/EtOH 3:2 in place of H₂O. Prior to ion-exchange chromatography, **6c** was purified by extraction with CH_2Cl_2 followed by evaporation.

¹⁾ Sample not identical with the one used for X-ray structural determination containing 1 H₂O molecule.

Successive concentrations yielded 13.0 g (60%) of **6c**. $[\alpha]_{589} = -290$, $[\alpha]_{546} = -590$, $[\alpha]_{365} = -1390$ ($c = 0.04$, $\text{H}_2\text{O}/\text{EtOH}$ 3:2, pH 6.3). VIS ($\text{H}_2\text{O}/\text{EtOH}$ 3:2, pH 6.4): 681 (162). CD ($\text{H}_2\text{O}/\text{EtOH}$ 3:2, pH 6.4): 615 (+1.34). Anal. calc. for $(\text{C}_{31}\text{H}_{39}\text{ClCuN}_3\text{O}_2)\text{ClO}_4$ (683): C 54.5, H 5.7, N 6.2, Cl 10.4, C/N 8.86; found: C 55.1, H 5.8, N 6.2, Cl 10.2, C/N 8.88.

2.7. 2,6-Bis[$\{(2S)-2-[(\text{benzyloxy})\text{methyl}]\text{pyrrolidin-1-yl}\}\text{methyl}\}\text{pyridine}$ (**3c**) was prepared as described in 2.3 using 0.646 g (0.95 mmol) of **6c** and $\text{H}_2\text{O}/\text{EtOH}$ 3:2 as solvent. Extraction of the ligand was achieved with hexane in place of CH_2Cl_2 : 0.445 g (97%) of **3c**. Pale yellow oil. $[\alpha]_{589}^{25} = +20.2$, $[\alpha]_{365}^{25} = +74.6$ ($c = 0.8$, H_2O , pH 1.5). UV: 263 (3700), 207 (24000). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.63–1.78 (*m*, 6 H); 1.96 (*m*, 2 H); 2.34 (*q*, 2 H); 2.87 (*m*, 2 H); 3.00 (*m*, 2 H); 3.39 (*q*, 2 H); 3.50 (*q*, 2 H); 3.92 (*q*, 4 H); 4.50 (*s*, 4 H); 7.23–7.31 (*m*, 12 H); 7.56 (*t*, 1 H). MS: 486 ($[M + 1]^+$).

3. *X-Ray Structure Determinations.* Details of data collection and structure refinement are given in Table 4. Data were collected using a *Stoe-AED2* four-circle diffractometer with graphite monochromated MoK_α radiation. Standard reflections were measured every h. The crystal $[\text{Cu}(\text{3c})\text{Cl}]\text{ClO}_4$ was covered with a thin layer of an epoxy resin. The structures were solved by direct methods or *Patterson-Fourier* methods using the NRCVAX system [13], which was also used for refinement and all further calculations. No absorption corrections were applied to the data.

Table 4. Crystal Data and Experimental Details

	$[\text{Cu}(\text{3a})\text{Cl}]\text{ClO}_4 \cdot \text{H}_2\text{O}$	$[\text{Cu}(\text{3b})\text{Cl}]\text{ClO}_4$	$[\text{Cu}(\text{3c})\text{Cl}]\text{ClO}_4$
Empirical formula	$(\text{C}_{17}\text{H}_{27}\text{ClCuN}_3\text{O}_2)\text{ClO}_4 \cdot \text{H}_2\text{O}$	$(\text{C}_{19}\text{H}_{31}\text{ClCuN}_3\text{O}_2)\text{ClO}_4$	$(\text{C}_{31}\text{H}_{39}\text{ClCuN}_3\text{O}_2)\text{ClO}_4$
M_r	521.9	531.9	684.1
Crystal colour/habit	blue plates	blue blocks	blue plates
Crystal system	orthorhombic	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Z	4	4	8
D_c [g/cm^3]	1.549	1.504	1.429
Linear absorption:			
Coefficient μ_{MoK_α} [cm^{-1}]	12.6	12.0	9.0
Crystal dimensions [mm]	0.57, 0.53, 0.26	0.53, 0.49, 0.46	0.65, 0.42, 0.23
Cell parameters (least-squares fit of):			
No. of reflections	17	17	20
2θ range [$^\circ$]	28–33	28–35	28–36
a [$\text{\AA}$]	11.207(1)	11.057(1)	11.724(1)
b [$\text{\AA}$]	11.628(1)	12.643(1)	30.346(5)
c [$\text{\AA}$]	17.174(2)	16.799(3)	17.871(2)
V [$\text{\AA}^3$]	2238.0(4)	2348.4(5)	6358.1(1)
Scan mode	ω/θ	ω/θ	ω/θ
$2\theta_{\text{max}}$ [$^\circ$]	50	50	50
h,k,l range	+13,+13,+20	+13,+15,+19	+13,+36,+21
No. of reference reflns.	3	3	3
Variation [%]	2	3	3
No. of unique reflns.	2255	2346	6210
No. of reflns. used in refinement	1919	1915	3484
x in $[I > x\sigma(I)]$	2.5	2.5	2.0
No. of parameters refined	271	280	775
R	0.051	0.043	0.075
wR	0.075	0.061	0.088
r in $w^{-1} = \sigma^2(F_o) + k(F_o^2)$	0.002	0.0011	0.0025
max shift/ σ ratio	0.062	0.015	0.174
Residual density:			
max [$\text{e}/\text{\AA}^3$]	0.71	0.30	0.63
min [$\text{e}/\text{\AA}^3$]	−0.47	−0.50	−0.48

In the crystals of $[\text{Cu}(\mathbf{3c})\text{Cl}]\text{ClO}_4$, there are two independent molecules per asymmetric unit. The routine MISSYM in NRCVAX [13] did not detect any extra symmetry. For all three compounds, H-atoms were included in calculated positions and held fixed ($U_{\text{iso}} = U_{\text{eq}}(\text{C}) + 0.01 \text{ \AA}^2$), they were regenerated after every second cycle of refinement. In $[\text{Cu}(\mathbf{3a})\text{Cl}]\text{ClO}_4 \cdot \text{H}_2\text{O}$, the OH protons could not be located from the difference map, they were included with $U_{\text{iso}} = 0.008 \text{ \AA}^2$ and held fixed. The H-atoms of the H_2O molecule of crystallization could not be located. Non-H-atoms were refined anisotropically by weighted full-matrix least-squares. Neutral complex-atom scattering in NRCVAX are from the International Tables for X-Ray Crystallography [14]. Selected interatomic distances and angles are given in Table 1. The numbering schemes used are illustrated in Figs. 1a–d, which were prepared using the program PLUTO [15]. Tables of the final positional parameters, complete distances and angles, and equivalent isotropic thermal parameters were deposited with the *Cambridge Crystallographic Data Center*, 12 Union Road, Cambridge CB2 1EZ, England. Further supplementary data is available from H. St.-E.

4. *Equilibrium Measurements*. 4.1. *Potentiometric Measurements*. The titrations were made under N_2 . Solvent was bidistilled H_2O (for ligands $\mathbf{3a}$ and $\mathbf{3b}$) or bidistilled $\text{H}_2\text{O}/\text{EtOH}$ p.a. 62.5:37.5 (for $\mathbf{3c}$). Concentrations of Cu^{2+} and ligands were $2 \cdot 10^{-3} \text{ M}$ for $\mathbf{3a}$ and $\mathbf{3b}$ and $1 \cdot 10^{-3} \text{ M}$ for $\mathbf{3c}$. The ionic strength was fixed at 0.1 by NaNO_3 .

4.2. *Spectrophotometric and Spectropolarimetric Measurements*. A series of 10-ml solns. were prepared, all containing $5 \cdot 10^{-3} \text{ M}$ $[\text{CuLCl}](\text{ClO}_4)$ ($\text{L} = \mathbf{3a}, \mathbf{3b}$, or $\mathbf{3c}$), in bidistilled H_2O (for $\mathbf{3a}$ and $\mathbf{3b}$) or bidistilled $\text{H}_2\text{O}/\text{EtOH}$ p.a. 7:3 (for $\mathbf{3c}$). The ionic strength was fixed at 0.1 by NaNO_3 . For each soln., the desired pH was obtained by adding 0.15N HCl or 0.03N NaOH. Solns. were thermostated at 25° for 1 day. After this time, UV/VIS and CD spectra of each soln. were measured, and its exact pH value was determined simultaneously.

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LISTE DES PUBLICATIONS

- 1°. **Enantioselective Formation of Amino Acids by Isomerization of Mixed Ligand Copper(II) Schiff-Base Complexes.**

Thierry Chuard, François Gretillat, and Klaus Bernauer, *Chimia* **1993**, 47, 215.

- 2°. **Synthesis of Three New Optically Active Triamines:**

2,6-Bis[[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl]pyridine, 2,6-Bis[[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl]pyridine, and 2,6-Bis[[(2S)-2-(benzyloxymethyl)pyrrolidin-1-yl]methyl]pyridine. **X-Ray Structure and Equilibrium Behaviour of Their Copper(II) Complexes.**

Klaus Bernauer, Thierry Chuard, and Helen Stoeckli-Evans, *Helvetica Chimica Acta* **1993**, 76, 2263.

Le texte complet du travail de thèse est disponible à la
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