57. Stereoselectivity in Reactions of Metal Complexes

Part XI[1])

2,6-Bis(pyrrolidin-2-yl)pyridine: Synthesis and Resolution of the *meso* and the Optically Active Isomers. Complex Formation with Copper(II) Ion in Aqueous Solution

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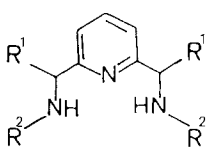
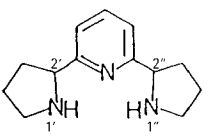
The new linear triamine 2,6-bis(pyrrolidin-2-yl)pyridine (**II**) has been synthesized, and the (*R,S*)-, (*R,R*)-, and (*S,S*)-isomers have been separated. Compared to other triamines showing a similar structure, these new ligands form very stable Cu^{2+} complexes. No significant difference is observed between the *meso* and the racemic forms for their binary or ternary mixed-ligand complexes with the amino acids alanine and proline.

1. Introduction. – In some of our previous work concerning asymmetric reactions involving copper(II) *Schiff*-base complexes, we reported the use of optically active C_2-symmetric triamines as auxiliary ligands [2–4]. These ligands, showing the basic framework **I**, gave quite high values of the enantiomeric excess (% ee) for certain of the reactions studied, but had the disadvantage that the chirality adopted in the complex by the two aliphatic N-atoms was not definitely fixed by the chiral centers of the molecule. The observed stereoselectivity of the reactions, therefore, could not be related in a straight-forward manner to the overall chirality of the reacting mixed-ligand *Schiff*-base complex. To overcome this problem, we decided to synthesize a series of more rigid ligands showing the basic structure **II**. For obvious stereochemical reasons, only the (1′*S*,1″*S*,2′*S*,2″*S*) and the (1′*R*,1″*R*,2′*R*,2″*R*) complexes can be formed from the reaction of metal ions with the racemic form of these ligands.



Ia $R^1 = R^2 = CH_3$, babp
b $R^1 = H$, $R^2 = Ph(CH_3)CH$, bpabp



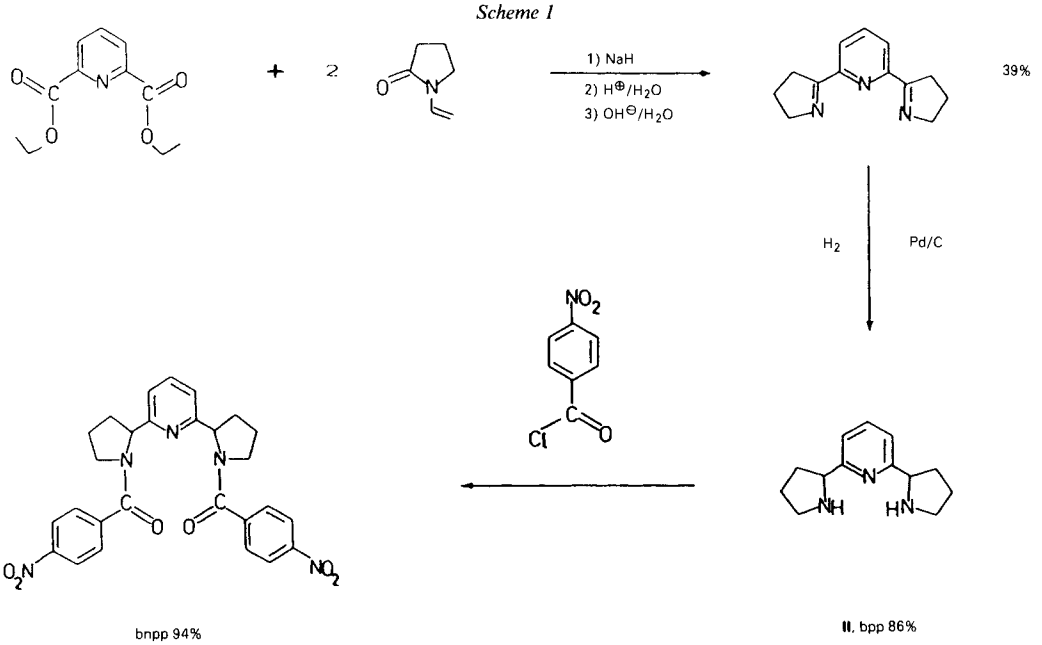
II, bpp

[1]) Part X, see [1].
[2]) Part of the Ph.D. thesis of *F.G.*

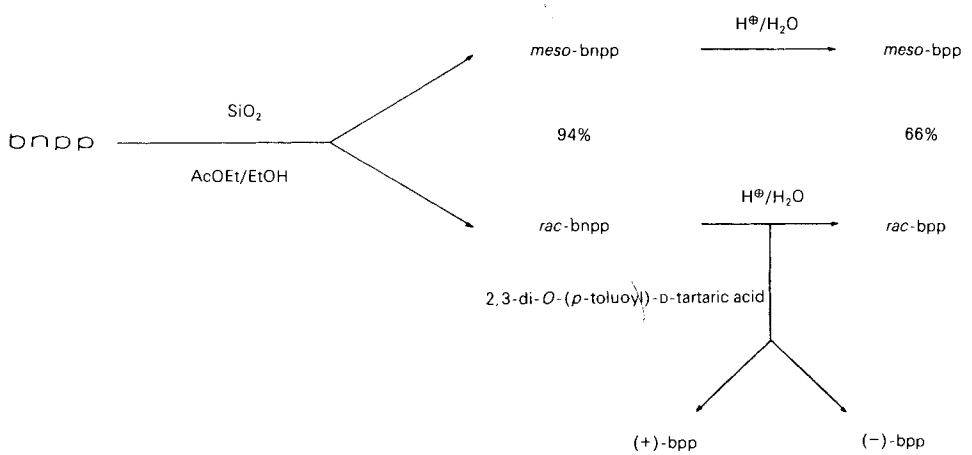
In the present paper, we report the synthesis of **II**, the separation of its three possible stereoisomers, and the study of binary and ternary mixed-ligand complex formation with Cu^{2+}.

2. Synthesis. – The mixture of *meso*- and *rac*-2,6-bis(pyrrolidin-2-yl)pyridine was prepared by an adaption of the method described by *Korte* [5] and *Jacob* [6] for the synthesis of isonicotine derivatives *(Scheme 1)*. The separation of the ligand into the *meso* and the *rac* form was achieved by chromatography according to *Scheme 2*.

Scheme 1



Scheme 2



3. Equilibrium Measurements. – The *Figure* shows typical titration curves for the system containing *meso*-bbp, *meso*-bbp/Cu^{2+} 1:1, and *meso*-bbp/Cu^{2+}/alanine 1:1:1.

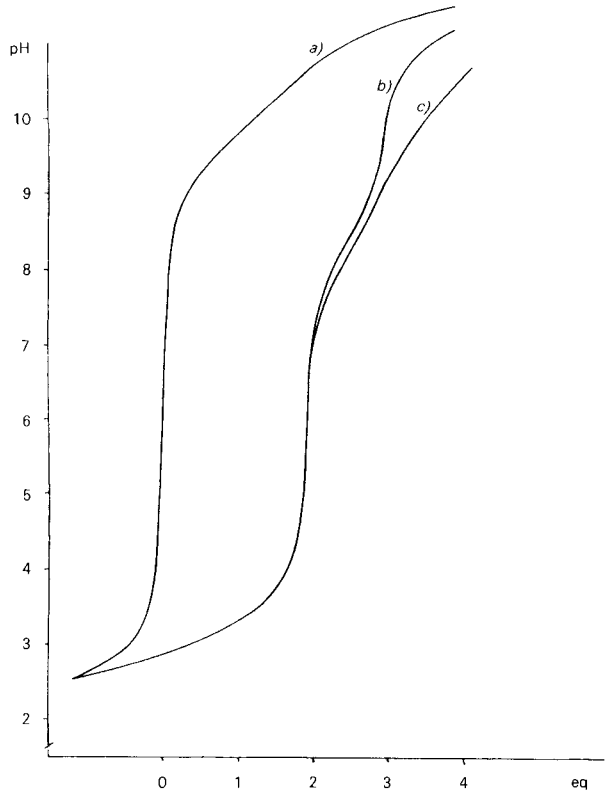


Figure. *Potentiometric equilibrium curves for* meso-*2,6-bis(pyrrolidin-2-yl)-pyridine* (L). *a*) ligand L alone $2.93 \cdot 10^{-3}$ M; $[HCl]_{tot}$ $9.13 \cdot 10^{-3}$ M; *b*) $[L]_{tot}$ and $[HCl]_{tot}$ as for *a*) with $[Cu^{2+}]_{tot}$ $2.84 \cdot 10^{-3}$ M; *c*) $[L]_{tot}$, $[HCl]_{tot}$, and $[Cu^{2+}]_{tot}$ as for *b*) with $[alanin]_{tot}$ $2.86 \cdot 10^{-3}$ M. Temp. 25.0°; $\mu = 0.1$ (KNO_3); eq = mol of NaOH/mol of ligand present.

From these potentiometric titrations, the corresponding equilibrium constants have been calculated for the *meso* and the *rac* forms. From the values given in *Table 1*, it can be seen that no significant difference exists between the two isomers for the binary complexes or for the mixed-ligand complexes with the two amino acids used.

Table 1. *Equilibrium Constants of the System* Cu^{2+}/meso-L *and* rac-L/*amino acid* (L = bpp). $T = 25°$; $\mu = 0.1$ (KNO_3).

Ion	Equilibrium	log K^{a})	
		meso	racemic
H^+	$H_2L/H \cdot HL$	9.46	9.39
	$HL/H \cdot L$	10.12	10.14
Cu^{2+}	$CuHL/H \cdot CuL$	3.26	3.03
	$CuL/Cu \cdot L$	16.70	16.80
	$CuL(H_2O)/H \cdot CuLOH$	8.26	8.49
	CuL(Ala)/CuL · Ala	3.77	3.74
	CuL(Pro)/CuL · Pro	3.79	3.92

[a]) Mean values from 4 titrations.

Table 2. *Equilibrium Constants of Tridentate Ligands with Cu^{2+} and their Mixed-Ligand Complexes with Amino Acids. $T = 25°$; $\mu = 0.1$ (KNO_3).*

Ligand L		pK_1	pK_2	log K_{CuL}	log K_{CuL}(aa)	Amino acid (aa)
Ib	(bpabp)[a])	7.49	8.57	10.50	4.92	Gly
					4.70	Ala
Ia	(babp)[b])	9.00	9.80	14.13	4.47	Gly
					4.02	Ala
rac-**II**	(*rac*-bpp)	9.39	10.14	16.80	3.74	Ala
					3.92	Pro

[a]) Values from [3]. [b]) See [4].

A comparison of the equilibrium constants observed for the new ligands with those obtained for the triamines of type **I** is shown in *Table 2*. It can be seen that the ligand bpp forms the most stable binary complex of the three ligands studied, its stability is also considerably higher than that of similar triamines, *e.g.* diethylenetriamine (log $K_{CuL} = 15.9$) [7], di(2-picolyl)amine (log $K_{CuL} = 14.4$) [7], or 2,6-bis(aminomethyl)pyridine (log $K_{CuL} = 15.2$) [8]. This high stability can in part be assigned to the higher basicity of the secondary amino groups, but might also be due to the highly rigid nature of the ligand in its coordinated form.

In contrast, binding of amino acids in the mixed-ligand complex shows the reversed tendency. Regarding the rather small differences between the mixed-ligand complexes of the *meso* and the racemic complex, the weaker capability of the [Cu(bpp)] complexes to bind amino acids should be attributed to electronic rather than to steric reasons.

These observations allow us to propose that although the activation of amino acids in [Cu(bpp)(amino acid)] complexes might be weaker than in other mixed [Cu(triamine)] complexes, due to the fact that the auxiliary ligand is more firmly bound to the metal center, the system should present appreciable advantages for asymmetric reactions as described earlier [2–4] on the stereochemical level and, at the same time, offer better opportunities for the design of a catalytic system.

Experimental Part

1. *General.* Optical rotations: *Perkin-Elmer* polarimeter *M 240*. ^{1}H-NMR spectra: *Bruker WP 200*. Mass spectra: *Normag R-30-10*. All the titrations were performed in bidistilled H_2O under N_2. Concentrations of Cu^{2+}, bpp, and amino acids were $5 \cdot 10^{-3}$ M. The ionic strength was fixed at 0.1 by KNO_3.

2. *Synthesis.* 2.1. *2,6-Bis(3,4-dihydro-2*H*-pyrrol-5-yl)pyridine.* A soln. of *N*-vinylpyrrolidin-2-one (36.6 g, 0.33 mol) and diethyl pyridine-2,6-dicarboxylate (34.8 g, 0.156 mol) in dry THF (200 ml) was added to 55% NaH (20.55 g; 0.471 mol) dispersed in dry THF (150 ml). After a few min, a strongly exothermic reaction started (violent evolution of H_2) which was controlled by cooling in an ice bath. When the evolution of gas had ceased, the mixture was heated under reflux for 30 min. The pale yellow product was hydrolyzed by addition of conc. HCl soln. (60 ml)/H_2O (90 ml). The THF was evaporated, a further portion of conc. HCl soln. (90 ml)/H_2O (180 ml) added, and the mixture refluxed overnight. After cooling, the soln. was made basic by the addition of NaOH (75 g) in H_2O (200 ml). The precipitated product was extracted with CH_2Cl_2. After evaporation, the brown to black residue was redissolved in EtOH/Et_2O/ligroine 4:3:3 (500 ml), placed on a 300-ml column of aluminium oxide *507c* (130 g), and eluted with Et_2O/ligroine 1:1. The eluate was concentrated and Et_2O added until a Et_2O/EtOH ratio of *ca.* 3:1 was obtained. From this soln., the hydrochloride was precipitated by dropwise addition of conc. HCl soln. (15 ml). The crystallized salt was filtered, air-dried, and dissolved in H_2O (200 ml). From the hot soln. (80°), the final product was precipitated by the addition of 0.5M NaOH. The crystals of the triamine were dried in a desiccator: 13.1 g

(39%). A small sample recrystallized from H_2O gave white crystals. M.p. 132°. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.04 (*q*, 4 H); 3.15 (*t*, 4 H); 4.14 (*t*, 4 H); 7.80 (*t*, 1 H); 8.13 (*d*, 2 H). MS: 213 ($M^{+\cdot}$).

2.2. *2,6-Bis(pyrrolidin-2-yl)pyridine (***II***; bpp).* At r.t., 2,6-bis(3,4-dihydro-2*H*-pyrrol-5-yl)pyridine (12 g, 56,3 mmol) in EtOH (300 ml) was hydrogenated for 15 h over 10% Pd/C (0.3 g) under 5 atm of H_2. After filtration and evaporation, the residue was distilled under high vacuum: 10,3 g (86%) of colorless oil. B.p. 96°/$5 \cdot 10^{-3}$ Torr. UV: 262 ($\varepsilon = 4400$). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.74 (*m*, 2 H); 1.85 (*q*, 4 H); 2.20 (*m*, 2 H); 2.60 (*s*, 2 H); 3.00 (*m*, 2 H); 3.22 (*m*, 2 H); 4.22 (*t*, 2 H); 7,17 (*d*, 2 H); 7.58 (*t*, 1 H). MS: 217 ($M^{+\cdot}$). Anal. calc. for $C_{13}H_{19}N_3$ (217): C 71.9, H 8.8, N 19.4, C/N 4.33; found: C 69.4, H 9.0, N 18.6, C/N 4.35.

2.3. *2,6-Bis[1-(*p*-nitrobenzoyl)pyrrolidin-2-yl]pyridine (bnpp).* *p*-Nitrobenzoyl chloride (20 g, 108 mmol) was added to a stirred soln. of freshly distilled bpp (**II**; 10 g, 46 mmol) in pyridine (40 g). After stirring at r.t. for 2 h and at 80° for 1 h, the mixture was cooled and CH_2Cl_2 (200 ml) and 2M HCl (100 ml) added. The mixture was transferred to a separatory funnel and shaken vigorously. The org. phase was washed twice with 2M HCl (100 ml), once with sat. Na_2CO_3 soln., and twice with H_2O (100 ml), dried ($MgSO_4$), and evaporated: orange solid (22.4 g, 94%). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.97 (*m*, 2 H); 2.07 (*m*, 4 H); 2.41 (*m*, 2 H); 3.55 (*q*, 2 H); 3.75 (*q*, 2 H); 3.97 (*t*, 2 H); 7.15 (*d*, 2 H); 7.22 (*d*, 2 H); 7.45 (*t*, 1 H); 7.78 (*d*, 2 H); 7.97 (*d*, 2 H); 8.29 (*d*, 2 H). MS: 515 ($M^{+\cdot}$).

2.4. *Hydrolysis of bnpp.* A soln. of bnpp (10 g, 19 mmol) in 70% H_2SO_4 soln. (50 ml) was heated to 150° for 30 min (these conditions must be rigorously followed, the product being substantially decomposed by longer reaction times). The mixture was cooled in an ice bath, diluted with H_2O (100 ml), and neutralized with NaOH (45 g) in H_2O (200 ml). The product was extracted with CH_2Cl_2, the org extract washed with H_2O, dried ($MgSO_4$), and evaporated and the residue distilled: bpp (**II**; 2.8 g, 66%).

3. *Differentiation of* meso- *and* rac-*bnpp.* A small sample of bnpp was introduced into a column of cellulose triacetate (*Merck*; 100 × 3 cm, *m* (dry phase) = 250 g) and eluted with H_2O/MeOH 1:5. The effluent was analyzed by UV (260 nm) and by polarimetry (436 nm). Two well separated bands were observed by UV, band *1* showed no optical activity. As band *2* was eluted, it showed initially a positive [α] which descended to zero and then became negative. Bands *1* and *2* were analyzed by TLC (silica gel F_{254}; AcOEt/EtOH 50:1): R_f 0.46 (band *1*) and 0.30 (band *2*). Thus the *meso* derivative should be eluted first on a column of silica gel, using AcOEt/EtOH 50:1.

4. *Separation of* meso- *and* rac-*bnpp.* A soln. of bnpp (50 g) AcOEt/EtOH 50:1 (700 ml) was adsorbed onto a column of silica gel *60* F_{254} (50 × 12 cm, *m* = 3000 g) and eluted with AcOEt/EtOH 50:1 (3.5 ml/min). After 2 days, *meso*-bnpp left the column, followed by *rac*-bnpp 2 days later. Three fractions were collected, pure *meso*-bnpp (31 g), a mixture (1 g), and pure *rac*-bnpp (15.2 g).

5. *Separation of the Enantiomers of* rac-*bpp.* (+)- and (−)-bpp were obtained by fractional crystallization of the acid salt formed with 2,3-di-*O*-(*p*-toluoyl)-L-tartaric acid: *rac*-bpp (5.05 g, 23.3 mmol) and (−)-2,3-di-*O*-(*p*-toluoyl)-L-tartaric acid (18.83 g, 46.4 mmol) were dissolved in H_2O (20 ml)/EtOH (100 ml) by heating. The soln. was left overnight in the refrigerator for crystallization. The crystals (12.0 g, 50%) were filtered and washed with EtOH. Recrystallization of the salt from H_2O (120 ml)/EtOH (140 ml) gave 10.13 g (42.4%) of (+)-bpp[(−)-2,3-di-*O*-(*p*-toluoyl)-L-tatrate]$_2$; $[\alpha]_{365} = -512$, $[\alpha]_{589} = -98$ ($c = 0.055$, MeOH). (+)-bpp was isolated by passing a sample through a small ion-exchange column (*Dowex-1*, OH^-). $[\alpha]_{365} = +378$, $[\alpha]_{589} = +126$ ($c = 0.1$, H_2O).

Enriched (−)-bpp (4.9 g, 22 mmol) obtained from the mother liquors as described in *2.4* and (+)-2,3-di-*O*-(*p*-toluoyl)-D-tartaric acid (18.3 g, 44 mmol) were dissolved in hot H_2O (16 ml)/EtOH (100 ml), and the soln. left in the refrigerator overnight. The crystals thus obtained (15.32 g, 66%) were recrystallized once from H_2O (150 ml)/EtOH (120 ml): 9.5 g (40%) of (−)-bpp [(+)-2,3-di-*O*-(*p*-toluoyl)-D-tartrate]$_2$; $[\alpha]_{365} = +521$, $[\alpha]_{589} = +99$ ($c = 0.055$, MeOH). (−)-bpp was obtained as indicated above for the (+)-isomer: $[\alpha]_{365} = -340$, $[\alpha]_{589} = -113$.

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