TRANSITION METAL COMPLEXES OF LIGANDS CONTAINING AZOMETHINE GROUP. IV.*

COPPER(II) SALICYLALDIMINATE COMPLEXES OF (S)-(+)-ASPARAGINE AND (S)-(+)-GLUTAMINE. APICAL INTERACTION OF (S)-(+)-ASPARAGINE

F. JURSÍK and B. HÁJEK

Department of Inorganic Chemistry,
Institute of Chemical Technology, 166 28 Prague 6

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The investigated complexes display optical activity in the region of *d–d* transitions due to the vicinal effect. Electronic absorption spectra of their solutions with λ_{max} between 640 and 655 nm correspond to a $Cu(N)_2(O)_2$ or $Cu(N)(O)_3$ chromophore. In alkaline medium the chromophore of [Cusal((S)-(+)-$AspNH_2$)X] (X is water or pyridine) is appreciably changed and an apical coordination of the carboxamidic nitrogen takes place in contrast to [Cusal((S)-(+)-$GluNH_2$)X]. The change is accompanied by a loss of optical activity. Transamidation both with the primary and the secondary amine leads in either case to the exchange of ligands. [Cusal((S)-(+)-$AspNH_2$). .Py] (Py is pyridine) when heated in absolute methanol looses the coordinated pyridine and dimerises. Under the effect of apical coordination the $CONH^{(-)}$ group of asparagine does not undergo alkaline hydrolysis in contrast to glutamine.

Metal complexes of Schiff's bases may be synthetised by two main routes. The first one[1] consists in the addition of metal ions into a solution of a Schiff's base prepared in situ (direct synthesis), while the second[2] consists in the reaction of the amine with the oxoligand complex (template reaction). While with monoaminomonocarboxylic acids both methods give identical results, in the case of aminodicarboxylic acids the synthesis of salicylaldimine copper(II) complex is dependent on pH, on the distance of both carboxyls, and also on whether the amino acid is optically active or racemic. In the case of (*S*)-(+)-aspartic acid direct synthesis leads to the hydrolysis of the reaction intermediate[3] (probably stereospecifically coordinated[4]) and the formation of copper(II) aspartate[4], without regard to the pH. Schiff's base metal complexes of amino acid derivatives undergo reactions (racemization, amidation, transamination, *etc.*) of which some are catalysed *in vivo* by pyridoxal containing enzymes[5–7]. It was established[8] that it is just the copper(II) complexes of aminodicarboxylic acids derivatives that display decreased reactivity both in the region of the α-carbon atom and on the carbonyl group. These facts depend on the conformation of the given complexes in which the side chains carrying the corresponding functional groups are arranged in pseudoaxial position[8].

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In this paper the preparation and the reactivity of the Schiff's base copper(II) complexes derived from amides are described. These ligands may undergo, in addition to the described reactions, activation on the amidic group which, in a favourable case, can then coordinate outside the plane of the donor atoms.

EXPERIMENTAL

(*S*)-(+)-Asparagine ($[\alpha]_D = +31°$ in 5M-HCl) and (*S*)-(+)-glutamine ($[\alpha]_D = +45°$ in 1M-HCl). Bis(salicylaldehydato)copper(II) was prepared according to[9]. Electronic absorption spectra were measured on an Optica-Milano CF-4 apparatus, infrared spectra (KBr technique) on a Perkin-Elmer spectrograph. Optical rotatory dispersion was measured on a Jasco-UV-5 spectropolarimeter.

Preparation of Complexes

A) Direct reaction: 0·01 mol of the corresponding amide was dissolved in 50 ml of water and 0·01 mol of salicylaldehyde was added to the solution, followed by as much methanol as necessary for a complete dissolution. The solution was heated at 60°C and additioned with $CuCO_3.Cu(OH)_2$. The unreacted carbonate was filtered off while hot and from the cooled filtrate the complex crystallised out which was recrystallised from 50% dioxan.

B) Template reaction: To a solution of 0·01 mol of amide in water bis(salicyladehydato) copper(II) (0·01 mol) was added at 50°C and the mixture heated for 30 minutes. After filtration and cooling the complex of the corresponding amide was obtained which was recrystallised.

[N-*Salicylidene*(*S*)-(+)-*asparaginatoaquo*]copper(II). For $C_{11}H_{12}N_2O_5Cu$ (315·7) calculated: 41·84% C, 3·83% H, 8·87% N; found: 41·94% C, 3·80% H, 8·85% N.

[N-*Salicylidene*(*S*)-(+)-*glutaminatoaquo*]copper(II): For $C_{12}H_{14}N_2O_5Cu.2\,H_2O$ (365·8) calculated: 39·39% C, 4·96% H, 7·66% N; found: 39·25% C, 5·02% H, 7·41% N.

When pyridine was added to the reaction mixture and this was concentrated in vacuo complexes with coordinated pyridine were obtained.

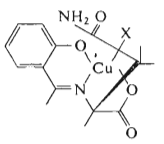
[N-*Salicylidene*-(*S*)-(+)-*asparaginatopyridino*]copper(II). For $C_{16}H_{17}N_3O_4Cu.3\,H_2O$ (432·9) calculated: 44·38% C, 5·36% H, 9·71% N; found: 44·20% C, 5·42% H, 9·90% N.

[N-*Salicylidene*-(*S*)-(+)-*glutaminatopyridino*]copper(II). For $C_{17}H_{19}N_3O_4Cu.3\,H_2O$ (446·9) calculated: 45·68% C, 5·64% H, 9·41% N; found: 46·00% C, 5·03% N, 9·40% N.

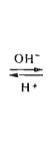
RESULTS AND DISCUSSION

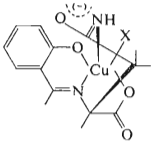
The prepared complexes are derived from ligands containing N and O as donor atoms in the molecule, and the complexes isolated from neutral medium correspond in their properties to a $Cu(N)(O)_3$ (*I*) or $Cu(N)_2(O)_2$ (*II*) chromophore. Under certain conditions a formation of complexes with a $Cu(N)_3(O)_2$ (*III*) chromophore may take place.

Electronic absorption spectra in the visible and the ultraviolet region are given in Table I. All chelates show a band (640 – 655 nm) in the lower-energy region corresponding to a *d–d* transitions. As ourc omplexes are such as have the d_{xy} orbital (Cu(II)) half occupied[10] these transitions produce a broad absorption band (Fig. 1).



I, X = H_2O
II, X = pyridine





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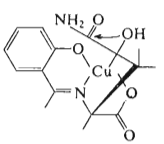

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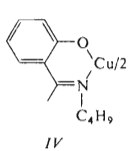

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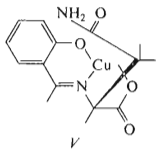

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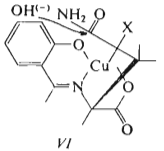

VI

The bands of higher energy (360–380 nm) correspond to $\pi \rightarrow \pi^*$ transitions on the azomethine chromophore[11]. In comparison with the uncoordinated ligand this band displayed a bathochromic shift which indicates an increased conjugation degree in the molecule[12]. Additional bands (240–270 nm) may be assigned to $\pi \rightarrow \pi^*$ transitions of benzenoid complexes[11]. The change of the chromophore from $Cu(N)(O)_3$ to $Cu(N)_2(O)_2$ is accompanied by a change of λ_{max} by 10 nm and by a simultaneous increase in the extinction coefficient, if the fourth coordination site of copper is occupied by pyridine. The lengthening of the amide side chain by CH_2 is practically without effect on the absorption maximum position.

TABLE I
Absorption Maxima in Electronic Spectra

Complex[a]	Solvent	λ_{max}, nm (log ε)
[Cusal(AspNH$_2$)H$_2$O]	40% dioxan	655 (2·01), 365 (3·64), 270 (4·07)
	0·1M-KOH	580 (1·96), 360 (3·65), 270 (4·01)
[Cusal(AspNH$_2$)Py]	50% dioxan	640 (2·07), 370 (3·66), 265 (4·14)
	0·1M-KOH	590 (2·00), 365 (3·66), 270 (4·02)
[Cusal(GluNH$_2$)H$_2$O]	50% dioxan	650 (2·00), 370 (3·64), 270 (4·09)
	0·1M-KOH	640 (1·85), 380 (3·77), 265 (3·88)
[Cusal(GluNH$_2$)Py]	50% dioxan	640 (2·07), 370 (3·66), 265 (4·14)
	0·1M-KOH	640 (1·92), 370 (3·69), 265 (4·11)

[a] AspNH$_2$ means (*S*)-(+)-asparagine, Py is pyridine, GluNH$_2$ is (*S*)-(+)-glutamine, sal means salicylaldehyde.

The complexes derived from (*S*)-(+)-asparagine and (*S*)-(+)-glutamine are optically active, while the optical activity of the chromophore is induced by chiral ligands. The rotation sign of the free ligand is negative within the whole measured range of the visible part of the absorption spectrum, while for complexes the rotation has positive values in the vicinity of 550 nm (Fig. 2). This indicates that the conformation of the coordinated ligand differs from the conformation of the Schiff's base itself. The complexes give a negative Cotton effect which is combined with a strong absorption in the 360 nm region. The negative Cotton effect in this region is found in all copper(II) complexes of the Schiff's bases of (L)-amino acids. The course of the rotatory dispersion is not affected by the type of ligand bound in the equatorial plane on the fourth coordination site of copper. In contrast to complexes of monoamino-monocarboxylic acids with Schiff's bases the complexes described loose optical activity in basic medium (0·1M-KOH) and racemize immediately.

(*S*)-(+)-Asparagine and (*S*)-(+)-glutamine may be coordinated either as bidentate or tridentate ligands. The trifunctional nature of these ligands leads to a flexidentate coordination because the $-CONH_2$ group contains two different donor atoms and therefore may be coordinated either by its amidic nitrogen or by oxygen. In the solid phase – as follows from the infrared spectra – probably neither of the atoms

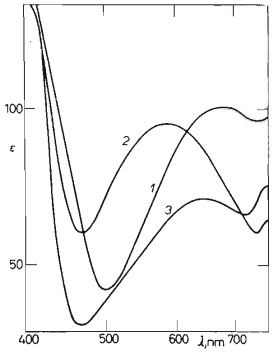

FIG. 1

Absorption Spectra

1 [Cusal(AspNH$_2$)H$_2$O] in 50% dioxan; *2* [Cusal(AspNH$_2$)H$_2$O] in 0·1M-KOH; *3* [Cusal(GluNH$_2$)H$_2$O] in 0·1M-KOH.

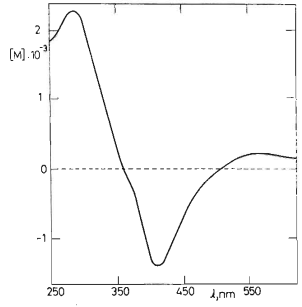

FIG. 2

Optical Rotatory Dispersion [Cusal((*S*)-(+)-AspNH$_2$)Py] (methanol)

mentioned is coordinated. In contrast to this chelates of (*S*)-(+)-asparagine, irrespective of whether the fourth coordination site of Cu(II) is occupied by molecule of water or pyridine, change their λ_{max} in alkaline medium from 655 (*I*) to 580 nm (*III*), or from 540 (*II*) to 590 nm (*III*) with a simultaneous change of the extinction coefficient. The isomerisation observed is reversible. Other absorption band maxima are not shifted. From this it follows that the shift of λ_{max} expresses the change of the ligand field due to the substitution of O by N. The same behaviour is also observed in bis(asparaginato)copper(II) in alkaline medium where λ_{max} is shifted from 620 to 590 nm[13]. The shift of the absorption band can take place only if the carboxamide group is coordinated with the copper atom similarly as in the case of (N-salicylideneglycylglycinato)copper(II)[14] the aqueous solution of which also shows a change in λ_{max} in alkaline medium. However, with respect to the nature of the nitrogen atom (—CON^- group) λ_{max} is 560 nm. Due to the coordination of the —$CONH_2$ group a labilisation of the amidic proton takes place (similarly as in peptide complexes an activation of the peptidic proton takes place[15]) followed by its easy splitting off in alkaline medium and subsequent coordination of the imino nitrogen. In principle an activation of the —$CONH_2$ group by coordination may take place in several ways. First, the —$CONH_2$ group could be coordinated in the *trans*-position of the same molecule. However the inspection of molecular models excludes this possibility, not to mention the fact that this structure would be more probable in the case of (*S*)-(+)-glutamine where a similar state was not observed. The dimeric structure with the coordination of the —$CONH_2$ group in the neighbouring molecule can also be excluded, because it would be equally possible even in the case of the complex of (*S*)-(+)-glutamine. In addition to this the agreement of λ_{max} in OH^- medium with λ_{max} of bis(asparaginato)copper(II) complex excludes this alternative. Hence, if these cases are excluded a single possibility remains, *i.e.* that the —CH_2—$CONH_2$ chain is coordinated (through the —$CONH_2$ group) by apical coordination (*III*). The different behaviour of the (*S*)-(+)-glutamine complex in which no shift of absorption maximum takes place in alkaline medium would also agree with this. The size of the chelate ring is also connected with the apical coordination, as is its effect on the probability of the axial coordination of the side-chain with the —$CONH_2$ group. The apical coordination of (*S*)-(+)-glutamine in the complex with Schiff's base would lead to the formation of a seven-membered, rather unstable ring. In this case a possible coordination in the second coordination sphere of the copper atom may be supposed, similarly as in the metal complexes of tautomeric Schiff's bases[16]. A number of facts speaks for an axial arrangement of the side chains carrying the carboxamide group. First, the substituents on the α-carbon atom may have a pseudoaxial or a pseudoequatorial character. In the case of copper(II) complexes of Schiff's bases derived from salicylaldehyde and (−)-propylenediamine a "1,3-interaction" between the —CH_3 group of propylenediamine and the substituents on the azomethine group[17] was observed. Even in the case of a hydrogen atom this interaction

is sufficient, so that the $—CH_3$ group of propylenediamine will assume a pseudoaxial conformation[17]. In our case too this will bring about a sterically preferred conformation with the hydrogen atom in the pseudoequatorial position, and on the other hand this forced pseudoaxial disposition of the $—(CH_2)_nCONH_2$ chain will support the apical coordination. In addition to this cases are known when aspartic acid or its amide bind with Cu(II) outside the donor atoms plane. Kirchner[18] prepared an octahedral copper(II) aspartate, Tsangaris and Martin[19] demonstrated that aspartic acid can be bound under formation of complexes with the coordination number 5 or 6, and Wellman and coworkers[20] observed that (*S*)-asparagine in the mixed glycine complex in alkaline medium coordinates at the fifth coordination site of the copper atom by apical coordination. The same must be true of the copper(II) complexes of Schiff's bases because the side chains do not issue from the trigonal nitrogen atom of the azomethine group, but from the sterically free (in comparison with the nitrogen atom) α-carbon atom of the amide. This apical coordination is theoretically possible in all instances when the coordination sites in the equatorial plane are occupied by a multidentate ligand with a polar group capable of coordination in the side chain. Another case, also leading to an apical coordination, is the combination of a tri- and a bidentate ligand, coordinated to a copper(II) atom[21].

A more substantial proof of the apical coordination of the amide group of (*S*)-(+)-asparagine would follow from the magnitude of the Cotton effect amplitude observed in the visible region of the absorption spectrum. Optical activity of the complexes is sensitive to the conformation of the chelate rings[20], because the side-chains carrying the group capable of apical coordination may shift the conformation equilibrium to the side of the conformer with pseudoaxial arrangement. This would result in an increased positive value of the Cotton effect amplitude[20]. However, under the conditions when a shift in λ_{max} takes place, *i.e.* in 0·1M-KOH, instantaneous racemisation takes place without the hydrolysis of the $—CONH_2$ group. The rate at which the (*S*)-(+)--asparagine complex racemizes is distinctly affected by the coordination of the $—CONH^-$ group, because under the same conditions N-salicylidene((*S*)-valinato)copper(II) does not racemize. The coordination of the $—CONH^-$ group probably facilitates the decrease in the electron density on the α-carbon atom.

Further reactions also depend on the proposed structure. We tried to transamidate the carboxamidic group with n-butylamine under the conditions described by Verter and Frost[22]. Within several minutes an exchange of the ligands took place under formation of *IV*. This occurred even when the reaction took place in dilute solution. Transamidation and the ligand exchange are two competitive processes. The rate of both of them is increased by the polarization of the azomethine group by coordination[23]. At a pH at which transamidation takes place the $—CONH_2$ group in the (*S*)-(+)-asparagine complex is coordinated with the carboxamide nitrogen, and the reaction which for this type of ligand requires the formation of an intermediate with the $—CONH_2$ coordinated with the oxygen atom is thus retarded. In addition to this the kinetic lability of the Cu(II) complexes and the strongly nucleophilic character of n-butylamine also play a role. Transamidation is a process

rather of a thermodynamic than a kinetic nature because the character of the products of this reaction depends on the basicity of the entering ligand[23]. Therefore, in our endeavour to decrease the nucleophilic activity of the amidating-reagent we also carried out the transamidation with dibutylamine. This reaction again rapidly led to a product the properties of which were analogous to those of the substance formed on reaction of bis(salicylaldehydato)copper(II) with dibutylamine. In view of the nature of the nitrogen atom it may be assumed that in this case the substance is of carbinolamine type.

Under the supposition of a sufficient activation of the amidic group its alcoholysis might be expected. However, this was in no case observed. On the contrary, heating of *II* in anhydrous methanol gave an insoluble substance, *V*, the elemental analysis of which showed that it did not contain pyridine. The infrared spectrum corroborated this fact. In addition to this the band about 1 600 cm^{-1} indicates that it is a substance of dimeric character[3]. This phenomenon was not observed in the case of complex (*S*)-(+)-glutamine.

Stabilisation towards OH^- ions is also connected with the coordination of the $—CONH_2$ group. While platinum(II) aspartate (which does not contain an electron depleting group) undergoes alkaline hydrolysis[24], this was not observed even in 0·1M-KOH in our case. In the case of the (*S*)-(+)-glutamine complex it was observed only after 24 hours. Transamidation, the same as hydrolysis of carboxamide, requires either a complex of the carbinolamine type[25] as intermediate, or a complex with the coordinated oxygen of the $—CONH_2$ group, with simultaneous participation of the external base (*VI*), or also an internal nucleophilic attack with the coordinated hydroxyl[26] (*VII*). However, under the conditions of the reaction neither *VI* nor *VII* can be considered as intermediates. The increased stability of the $—CONH_2$ group toward OH^- ions in the (*S*)-(+)-asparagine complex is a consequence of the apical coordination of the carboxamidic nitrogen already discussed. Indeed, it was observed that the coordination of peptides with the nitrogen atom of the $—CON^-$ group increases the stability of these ligands towards the OH^- ions[27,28]. The different behaviour of the platinum(II) asparaginate may be explained by a greater ligand field stabilisation of the square-planar arrangement of the Pt(II) complex, in comparison with the Cu(II) complexes[29]. In contrast to this the low reactivity of the $—CONH_2$ group of the coordinated (*S*)-(+)glutamine is due to the appreciable distance of this group from the activating center (azomethine groups), causing its reactivity to be low, similarly as in the case when the amide is bound as a mono-dentate ligand.

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