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

SYNTHESIS AND REACTIONS OF COPPER(II) COMPLEXES OF DICARBOXYLIC ACIDS MONOESTERS**

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On reaction of bis(salicylaldehydato)copper(II) with corresponding monoesters of (*S*)-(+)-aspartic acid or (*S*)-(+)-glutamic acid, or on reaction of the *in situ* formed Schiff's base of salicylaldehyde and Cu^{2+} ions square-planar complexes of Schiff's bases were prepared. The ester group in the side chain had no effect on the labilization of α-proton and therefore the complexes were isolated as optically active material. The ω-ester groups do not undergo an ester exchange or amidation. The low reactivity of both the α-proton and the carboxyl group is a consequence of the complex conformation. The re-esterification of the complexes of (*S*)-(+)-aspartic and (*S*)-(+)-glutamic acid takes place with the loss of coordinated water and formation of a dimer which may be transformed to its monomer with pyridine. The complexes containing pyridine on the fourth coordination site also do not undergo an ester exchange.

Due mainly to their reactivity, metal complexes of Schiff's bases of type *Ia* have been appreciably investigated. Pfeiffer and coworkers[3] found that copper(II) complexes of the mentioned type underwent reactions both on the ester carbonyl group, *i.e.* hydrolysis and transesterification, and on the α-carbon of amino acid, *i.e* racemization or also oxidation. In the complexes of Schiff's bases both these reacting parts are sufficiently activated in comparison with the ligands alone, so that they may also in principle undergo amidation or transamidation, as Verter and Frost[4] found. Several mechanisms were proposed for these reactions, based on an inductive electron shift[5], formation of a lactone intermediate[4], dissociation of the complex with subsequent coordination of the acyl oxygen of the ester group[6], and finally utilizing the internal nucleophilic attack in the carbinolamine intermediate[7].

As for the racemization of the esters of optically active amino acids, this is dependent on the presence of groups causing an electron shift, and it takes place *via* the carbanion *II* which is stabilized by enolate resonance[8]. In contrast to this the complexes of type *IIIa* are optically stable and undergo racemization only when another group capable of causing an electron shift[8] is present in the molecule.

* Part I and II: see refs[1,2].

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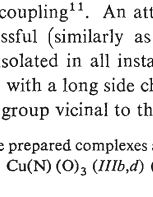
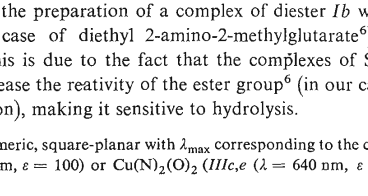
In this paper the preparation and the properties of complexes *IIIb*—*IIIe* are described, which have a structure between *Ia* and *IIIa*, and the study of which might contribute to the knowledge of the factors which affect both the reactivity of the terminal functional groups and the optical activity of the complexes.

Complexes *IIIb* and *d* were prepared by a direct reaction of a Schiff's base (prepared *in situ*) and Cu^{2+} ions, and also by a so-called template reaction[9] from bis(salicylaldehydato)copper(II) and hydrochloride of the corresponding monoester. The reactions were carried out in non-aqueous medium. The nature of the products is independent of the presence of the amount of anhydrous sodium acetate in the reaction mixture. The reaction is sufficiently fast so that after 5 minutes the reaction mixture contained only the ester complex. In constrast to a similar reaction of amino acids alone, which in the case of *IIIf* led to hydrolysis of the reaction intermediate[2], an analogous reaction was not observed due to the small coordination ability of the ester group. The difference in behaviour between the complex of the Schiff's base of (*S*)-(+)-aspartic acid and the complex of the ester is thus an additional proof of the three-functional nature of (*S*)-(+)-aspartic acid in the reaction intermediate, which — in accordance with the mechanism of formation of Schiff's bases complexes (equilibrium displacement[9]) — facilitates its hydrolysis[10]. In the case when the reaction was carried out in the absence of water (see Experimental) a product insoluble in solvents of low coordination ability (for example $CHCl_3$) was isolated, the infrared spectrum of which displayed a splitting of the band at 1630 cm^{-1} and the magnetic moment of which had a subnormal value ($\mu_{eff.}$ = 1·34 B. M. at 298 K). These circumstances indicate a dimeric structure of *IV* (n = 1 or 2) with an antiferromagnetic spin coupling[11]. An attempt at the preparation of a complex of diester *Ib* was unsuccessful (similarly as in the case of diethyl 2-amino-2-methylglutarate[6]); *IIIb* was isolated in all instances. This is due to the fact that the complexes of Schiff's bases with a long side chain increase the reativity of the ester group[6] (in our case the ester group vicinal to the α-proton), making it sensitive to hydrolysis.

The prepared complexes are monomeric, square-planar with λ_{max} corresponding to the chromophore Cu(N) $(O)_3$ (*IIIb,d*) (λ = 660 nm, ε = 100) or $Cu(N)_2(O)_2$ (*IIIc,e* (λ = 640 nm, ε = 120):



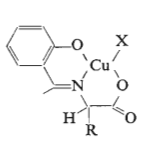
Ia, $R^1 = R^2$ alkyl, aryl
Ib, $R^1 = -CH_2.COOCH_3$
$R^2 = CH_3$



II, $R^1 = R^2$ alkyl, aryl

and have optical activity in consequence of the vicinal effect in the region of *d*—*d*-transitions, *IIIb*: $[M]_{578} = +336°$, $[M]_{546} = +129°$, $[M]_{436} = -2\,020°$, $[M]_{405} = -1\,820°$, $[M]_{365} = -3\,210°$; *IIId*: $[M]_{578} = +202°$, $[M]_{546} = +135°$, $[M]_{436} = -1\,960°$, $[M]_{405} = -490°$, $[M]_{365} = -2\,540°$ (in 50% dioxan).

In spite of the fact that these complexes contain groups —CH=N—, —$COOCH_3$ causing electron shifts, *i.e.* the presence of which represents a necessary condition for racemization, and in spite of the fact that they were prepared under such conditions when a rapid loss of optical activity takes place in *Ia*, they are optically active. Only the weakening of the α-C—H bond is connected with the presence of the mentioned groups, which leads to a loss of proton and the formation of a very reactive species the reprotonation of which results in racemization. The results show that the —$COOCH_3$ group located in the side chain is without any effect during the reaction and that the complexes display optical activity similarly as complexes *IIIa,f,g*[8,12]. Only at higher pH (≈ $1\cdot10^{-3}$M-KOH in 95% methanol) racemization takes place the rate of which is not affected by the distance of the —$COOCH_3$ group (this racemization in 95% methanol is not accompanied by the hydrolysis of the ester group). In this respect the behaviour of the complexes *IIIb—e* is the same as the behaviour of salicylidene-((*S*)-(+)-valinato) copper(II) (type *IIIa*). From this it follows that the ester group protruding from the chelate ring has no labilizing effect. A much more effective group labilizing the α-proton in complexes of the type *IIIa* and *g* is the NO_2 group, while its effect depends on its location on the aromatic ring of the Schiff's base[13]. Optical stability is related to the conformation *IIIb—e*, because the bonds to which the conformation permits an arrangement perpendicular to the plane of the π-system are cleaved easily, which is connected with an important increase of the delocalization energy of the π-system[14]. The coordination of the carboxyl in these complexes keeps the conformation of the chelate ring, containing the α-carbon atom in a less advantageous position (in comparison with *Ia* where the



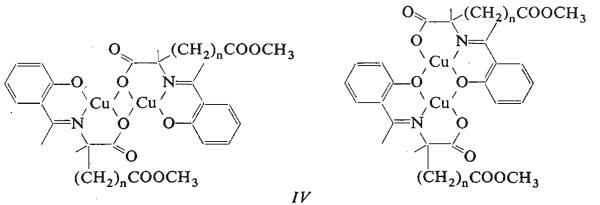
IIIa, R^1 = alkyl, aryl; X = H_2O, pyridine
IIIb, R^1 = —CH_2COOCH_3; X = H_2O
IIIc, R^1 = —CH_2COOCH_3; X = pyridine
IIId, R^1 = —$(CH_2)_2COOCH_3$; X = H_2O
IIIe, R^1 = —$(CH_2)_2COOCH_3$; X = pyridine
IIIf, R^1 = —CH_2COOH; X = H_2O, pyridine
IIIg, R^1 = —$(CH_2)_2COOH$; X = H_2O, pyridine

free rotation around the N—α—C bond keeps the α-proton in an optimum position) for an internal nucleophilic attack by the OH group of the carbinolamine[7]. In addition to this the presence of the $—CH_2$-group in the side chain of *IIIb–e* prevents the enolate resonance stabilisation of the carbanion formed.

The dependence of the optical rotation sign on the solvent used is also connected with the conformation of the chelate ring formed by the amino acid. In anhydrous methanol optical rotation has a negative value in the whole range of the visible part of the spectrum: *IIIb*: $[M]_{578} = -296°$, $[M]_{546} = -344°$, $[M]_{436} = -1\,280°$, $[M]_{405} = -1\,280°$, $[M]_{365} = -1\,280°$; *IIId*: $[M]_{578} = -338°$, $[M]_{546} = -487°$, $[M]_{436} = -3\,120°$, $[M]_{405} = -3\,120°$, $[M]_{365} = -3\,120°$.

Different rotation in anhydrous medium is caused by the loss of coordinated water at the fourth coordination site of the cooper atom (complexes with coordinated pyridine do not behave in this manner), which is a sufficiently fast process (*vide infra*). Dehydration leads to the dimer *IV* in which the four-membered ring forming a $—Cu—O_2—Cu$-bridge decreases the degree of the puckering of the chelate ring formed by the N—C—C—O atoms in comparison with *IIIb* and *d*.

Re-esterification is correlated with increased reactivity of the carbonyl group in the complexes of Schiff's bases. Complexes *Ia* undergo ester exchange the rate of which depends on the distance of the carbonyl group from the azomethine group. With increasing distance the re-esterification rate decreases[6]. This indicates that the electron shift caused by the —CH=N— group, supposed by Martell and Calvin[5], plays a certain role (the IR band due to the $—COOCH_3$ group vibration in *IIIb* and *d* is shifted towards lower frequencies by $10\,cm^{-1}$. It seems that this value does not correspond to a possible coordination of the acyl oxygen of the ester group[15]). The inductive shift is also manifest during hydrolysis of β-ethyl ester of (*S*)-(+)-aspartic acid in the presence of Cu^{2+} ions[16]. On heating *IIIb* in anhydrous ethanol a solid product separated in the course of 30 minutes, the elemental analysis, infrared spectrum (splitting of the band about $1\,630\,cm^{-1}$) and insolubility in $CHCl_3$ of which show that it must be a substance of dimeric nature (*IV*). Dehydration and re-esterification are two competitive processes while the rate of the second depends – as was already said – on the distance of the carbonyl group from the —CH=N— group.



IV

In the case of *IIIb* and *d* this distance is large, causing the loss of the coordinated water to be faster than the ester group exchange; the result is a dimer formation. The —Cu—O_2—Cu-bridge in *IV* is rather stable because on heating *IV* ($n = 1$ or 2) in aqueous methanol no monomeric, chloroform soluble *IIIb* or *d*, could be obtained. On the contrary, under the effect of pyridine substance *IV* is changed to *IIIc* or *IIIe* without the ester group hydrolysis taking place. This group is quite inert in *IIIb–e* and does not undergo hydrolysis even at elevated temperature, or re-esterification. Hydrolysis is immediate only in aqueous 0·1M-KOH. In the case of *IIIc* re-esterification leads to the isolation of impure substance the infrared spectrum of which contains in addition to the absorption band due to —$COOCH_3$ (1 730 cm^{-1}) also another band of lower intensity at 1 690 cm^{-1}. The absence of a maximum in the 3 200 cm^{-1} region indicates that the structure of the isolated substances is not that of a carbinolamine with added ethanol on the azomethine group. The —$COOCH_3$ group in *IIIe* also does not undergo re-esterification; in contrast to *IIIc* the starting substance (*IIIe*) was isolated. Complexes of the Schiff's bases derived from esters of diaminocarboxylic acids[4] also do not undergo transesterification.

An attempt at amidation of the ester group with n-butylamine under the conditions given by Verter and Frost[4] leads in the case of *IIIb–e* to the formation of N,N'-bis-(salicylidene-n-butyliminato)copper(II). This is a consequence of the polarization of the azomethine group by coordination during which the carbon atom with an electron deficit reacts with the strongly nucleophilic n-butylamine[4,17]. In addition to this the kinetic lability of Cu(II) complexes and the low reactivity of the ester group also play a role.

The observed low reactivity of the carbonyl group cannot be ascribed to unsufficient electron shift caused by the azomethine group. Houghton and Pointer[6] successfully re-esterified the ester group in complexes of type *Ia*, having the same position of the —$COOR^2$ group (β and γ) as in *IIIb* or *d*. Similarly the ester group in the copper (II) complex of the Schiff's base of glycylglycine also undergoes transesterification[18]. The reactivity both on the α-carbon and on the carbonyl group in the complexes of Schiff's bases depends, as was indicated earlier, on the presence of groups causing an electron shift, as well as on the conformation of the complex. The activation of the reacting centers[14] is also connected with conformation, because the reacting groups must be both activated by the π-system of the aromatic ring, and located in optimum position with respect to the nucleophilic group. Coordination of the carboxyl, which produces a decrease in free rotation around the =N—C— bond, does not fulfil these requirements. Also in complexes *IIIb–e* the side chains arrange themselves in axial positions, (a minimum of interactions[19]) due to non-bonding interactions, which, however, excludes an internal nucleophilic attack on the carbonyl group. Any other explanation is improbable because the structure of complexes excludes the mechanims supposing a coordination of the acyl oxygen[6] or the formation of a lactone-type intermediate[4].

EXPERIMENTAL

Apparatus and chemicals used: Hydrochlorides of β-methyl ester of (*S*)-(+)-aspartic acid ($[\alpha]_D$ +30° in methanol) and γ-methyl ester of (*S*)-(+)-glutamic acid ($[\alpha]_D$ +13·7° in methanol), and dimethyl ester of (*RS*)-aspartic acid were prepared from amino acids (Reanal, Budapest) according to[20,21]. For the preparation of bis(salicylaldehydato)copper(II) the procedure according to[22] was employed. Salicylaldehyde and n-butylamine (Lachema) were distilled before use.

Electronic absorption spectra were measured with CF-4 apparatus (Optica, Milano), infrared spectra in KBr on a Perkin-Elmer Type 325 spectrograph. For optical rotation measurement polarimeter Opton (German Fed. Republic) was used. Chromatography was carried out on thin layers of silica gel (Silufol UV 254, Kavalier, Czechoslovakia) with 70% propanol.

Preparation of IIIb *and* d: To a solution of 0·01 mol of the corresponding methyl ester in 50 ml of methanol 0·01 mol of bis(salicylaldehydato)copper(II) and 0·01 mol of anhydrous sodium acetate were added and the reaction mixture heated under stirring at 60°C for 15 minutes. Water (10 ml) was then added and the reaction mixture evaporated *in vacuo* to dryness. The residue was extracted several times with chloroform in which only the complex of the methyl ester dissolves. On evaporation of the chloroform extract to dryness a green substance was obtained. If no water was added during the reaction the major part of the complex remained in the form of *IV*.

Complexes may be also prepared according to Pfeiffer and coworkers[3] on reaction of 0·01 mol of monoester hydrochloride, 0·01 mol of salicylaldehyde, 0·01 mol of copper(II) acetate, and 0·01 mol of anhydrous sodium acetate in methanol. Further procedure is the same as in the preceding case.

Preparation of IIIc *and* e: The complexes of this type may be prepared by any of the mentioned methods in pyridine as medium, or from *IV* on reaction with pyridine.

Transesterification: 200 mg of *IIIb* or *e* were dissolved in absolute ethanol and refluxed for 12 h. After cooling the reaction mixture was evaporated *in vacuo* to dryness and a green substance was isolated, and in the case of *IIIe* its elemental analysis was identical with the analysis of the initial complex. In the case of *IIIb* the substance which separated during the reaction was filtered on a sintered glass filter and dried in air.

TABLE I
Elemental Analyses of the Prepared Complexes

Type	Compound	M.w.	Calculated			Found		
			% C	% H	% N	% C	% H	% N
IIIb	$C_{12}H_{13}CuNO_6$	330·8	43·57	3·96	4·24	43·37	4·09	4·22
IIIc	$C_{17}H_{16}CuN_2O_5$	391·9	52·10	4·12	7·15	52·29	4·07	7·09
IIId	$C_{13}H_{17}CuNO_7$	362·8	43·03	4·72	3·86	43·17	4·49	3·97
IIIe	$C_{18}H_{18}CuN_2O_5$	405·9	53·26	4·47	6·90	53·37	4·56	6·72
IV $n = 1$	$C_{12}H_{11}CuNO_5$	312·8	46·08	3·55	4·48	46·21	3·83	4·30
IV $n = 2$	$C_{13}H_{13}CuNO_5$	326·8	47·78	4·01	4·28	47·80	3·94	4·40

Amidation: 200 mg of *IIIc* or *e* were heated in 10 ml of n-butylamine. After several minutes the presence of N,N'-bis(salicylidene-n-butyliminato)copper(II) could be proved in the reaction mixture.

Hydrolysis: 200 mg of *IIIc*, or also *IIIe*, were refluxed in 50% dioxan for 24 h. Even after such prolonged heating hydrolytic products could not be proved chromatographically in the mixture.

Elemental analyses of the prepared complexes are listed in Table I.

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