Potentiometric Study of Enantioselective Effects in α-Amino Acid Complexes of Copper(II)

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Abstract

Using the MINIQUAD-75 program, stability constants of heteroligand (ternary) copper(II) complexes with N-alkylated derivatives of valine and proline or hydroxyproline were evaluated from potentiometric titration data. In the majority of combinations, heteroligand complexes appear to be the favoured species at equilibrium with the two corresponding homoligand complexes. The extent of this disproportion reaction depends strongly on the optical configuration of the constituent amino acid ligands, which implies that enantioselectivity is a common feature in copper complexes with N-alkylamino acids.

Introduction

Enantioselective effects, the difference in the kinetics or thermodynamics of interaction of a chiral reagent with two enantiomeric structures [1], play an important role in biochemistry, chemistry of high molecular compounds, coordination chemistry, and other disciplines. Studies into enantioselectivity effects in coordination compounds have gained special interest during the last decade, owing to the ligand-exchange chromatography method for resolving racemates [2]. A number of studies along this line (basically on the complexes with α-amino acid ligands) [3–5] have been performed, but the authors have failed to consider systematically the influence of N-alkyl substituents in the amino acid ligands. In our earlier works on square planar copper(II) complexes [6, 7] we pointed out the significance of this factor for displaying enantioselective effects.

We have recently [8] discussed the influence of N-alkyl substituents in the molecules of α-amino acid ligands on enantioselective effects in the homoligand (bis-amino acid) complexes of Cu(II). The present paper considers the results of studying enantioselective effects in heteroligand (mixed ligand) complexes involving N-alkyl-α-amino acids. When studying heteroligand structures, a stepwise introduction of alkyl substituents into amino groups of a square planar complex can be followed systematically, which provides additional information concerning enantioselective effects in these systems.

Experimental

Most amino acids were commercial reagents ('Reanal' Hungary) and were used without additional purification. N-alkyl derivatives of these amino acids were obtained by the techniques described in [9]; their analytical features corresponded to the literature data.

The solutions of amino acid ligands for potentiometric titration were prepared by dissolving accurately-weighed portions of the substance in distilled water.

The solution of copper perchlorate was prepared from the commercial poduct $Cu(ClO_4)_2 \cdot 6H_2O$ of 'chemically pure' grade, and its titer was established trilonometrically using murexide.

The solution of carbonate-free sodium hydroxide was prepared by dissolving metal sodium in degassed distilled water under argon atmosphere. The normality of NaOH solution was determined by potentiometrical titration with a hydrochloric acid solution prepared from fixanale.

A 1 M solution of KNO_3 prepared from the commercial preparation of 'chemically pure' grade was used as a background electrolyte solution.

Titration was performed on an OP-211 pH-meter ('Radelkis', Hungary) with OP-7183 and OP-8303 electrodes (produced by the same company), in a 50-ml vessel under argon at 25 ± 0.1 °C.

The alkali was added by a microburette SBR-2 ('Radiometer', Denmark) in 0.05 ml portions.

The ratio of the reagents at titration metal: ligand I: ligand II was usually chosen to be 1:1:1 and 2:3 titration curves were recorded for each system, with 40–50 points in each curve, in the pH range from 3 to 10. In systems with heteroligand complexes of low stability addition titrations were performed with other ratios of the reagents.

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The data obtained were processed on an EC-1060 computer using the MINIQUAD-75 program [10], which made it possible to compute simultaneously up to 20 different complex forms of the $M_mN_nP_pQ_qR_r$ composition, where M and N are metals, P and Q are ligands, R are protons or hydroxyls (in the latter case the index r is negative).

Results and Discussion

I. Composition of the Complexes

The stability constants for the heteroligand complexes examined are given in Table I. To describe these systems it is often sufficient to take into account only heteroligand neutral and monoprotonated complexes, where R is generally less than 1%. For sterically overloaded ligands, as was the case with homoligand systems, the solution also contains the hydroxo-form $CuL_AL_B(OH)$. No bis-hydroxo-form was observed within the studied pH range, and the R-factor was not improved when the complexes $CuL_AL_B(OH)_2$ were taken into account.

A comparison of the composition of the heteroligand complexes with that of the corresponding homoligand systems [8] shows that both are described by similar types of complex sets, but in the first case the protonated forms are more common than in the homoligand complexes. Sometimes neither of the ligands forming heteroligand protonated structure display formation of protonated homoligand complexes within the same pH range. For this reason, in most complexes we cannot localize the proton on a specified ligand in the heteroligand complex. In the case of heteroligand complexes containing proline type ligands that are known to possess higher basicity, one cannot be sure that the heterocyclic nitrogen is the bonding site for the proton since proline and its derivatives simultaneously display definitely higher affinity towards copper ions.

II. Stability Constants of Heteroligand Complexes

As it was already mentioned, the study of heteroligand complexes allows one to introduce the substituents into the complex molecule gradually, which helps to find a number of new features in the formation of these structures which were not observed for homoligand complexes. Indeed, in the studies of homoligand complexes we noted that the introduction of N-alkyl substituents decreases the stability of the resulting complexes, while in the case of the heteroligand complexes the situation is more complicated. The complex stability in proline-N-alkylated valine or hydroxyproline-N-alkylated valine passes through the maximum which corresponds to N,N-dimethylvaline (Table I). As for the complexes of N-benzylproline and allo-hydroxyproline, maximum stability is observed for mono-substituted valine ligand, N-benzylvaline. However, for heteroligand complexes of N-benzylated hydroxyproline and N-benzylated allo-hydroxyproline any substituent introduced into the valine ligand decreases the complex stability. Similarly, introduction of the benzyl substituent into the heterocyclic ligand of a heteroligand complex always destabilizes the complex when compared to the corresponding non-substitued analog.

Thus, comparing stability of the various heteroligand complexes we can conclude that two N-alkyl substituents, if they are localized at different ligands, do not necessarily result in the destabilization of the complex (it should be taken into account that heterocyclic amino acids are already N-alkyl-substituted). However, introduction of both substituents into the same ligand often diminishes the stability of the complex as compared to its non-substituted analog.

Most probably, this situation is due to strong steric interactions of the N-substituents with water molecules coordinated on two axial positions of the complexes: when both substituents are located at different ligands, each of them can take an equatorial position in the distorted five-membered chelate ring, thus avoiding interactions with the apical ligand. Positive induction effects of the alkyl substituents may even bring about additional stabilization of the copper–nitrogen coordination bond as compared to non-substituted amino group. When both substituents are placed at one nitrogen, one of them should inevitably take the axial position, and its steric interaction with the apical ligand results in destabilization of the complex.

Interesting information about stabilization or destabilization of the heteroligand structure compared with the initial homoligand compounds can be provided by the examination of the disproportionation constants for the following equilibrium:

$$MA_2 + MB_2 \xrightleftharpoons{K^2_{MAB}} 2MAB \qquad (1)$$

For a purely theoretical distribution of ligands A and B between the complexes, $K^2_{MAB} = 4$ ($\log K^2_{MAB} = 0.6$), and the shift of this value towards greater or smaller values, characterizes the preference of the formation of heteroligand or homoligand complexes respectively. Since the compounds in the right and left-hand parts of eqn. 1 are close in their chemical structure, the deviation of K^2_{MAB} from the theoretical value can be attributed to the changes in the intensity of steric interligand interactions in the complexes under consideration.

Unfortunately, the value of K^2_{MAB} cannot be determined if one of the initial homoligand bis-complexes does not exist under similar conditions (for instance, due to strong interligand interactions).

TABLE I. Stability Constants of Heteroligand Copper(II) Complexes with Amino Acid Ligands.

Amino acid		S-Val				S-Me Val			
		log β_{1110}	log β_{1111}	log $\beta_{111\text{-}1}$	R%	log β_{1110}	log β_{1111}	log $\beta_{111\text{-}1}$	R%
Pro	*S*	14.66(14)			0.7	15.58(15)			7
	R	14.86(18)			2	15.56(16)			7
Hyp	*S*	15.07(2)	19.71(2)		0.2				
	R	14.49(3)	19.24(3)		0.2				
aHyp	*S*	16.05(14)	20.45(20)		1	16.80(8)	21.60(6)	6.58(11)	0.6
	R	15.76(12)	20.34(16)		1	16.85(9)	21.55(5)	6.37(10)	0.9
BzlPro	*S*	13.94(12)		5.59(20)	3				
	R	13.22(67)		4.94(55)	5				
BzlHyp	*S*	14.81(7)		7.98(26)	2				
	R	14.67(8)		7.32(48)	3				
BzlaHyp	*S*	15.28(2)	19.31(6)	4.87(4)	0.4	15.09(5)		4.91(9)	1
	R	15.79(2)	20.06(3)	5.34(4)	0.6	15.29(6)		4.99(8)	1

S-BzlVal				S-Me$_2$Val				S-Bzl, MeVal			
log β_{1110}	log β_{1111}	log $\beta_{111\text{-}1}$	R%	log β_{1110}	log β_{1111}	log $\beta_{111\text{-}1}$	R%	log β_{1110}	log β_{1111}	log $\beta_{111\text{-}1}$	R%
15.76(16)	21.20(9)	9.21(28)	1	16.56(4)			0.4	12.53(27)			2
15.68(19)	21.22(9)	9.29(29)	1	13.59(23)			2	13.59(23)			2
15.29(8)	20.45(5)	8.17(36)	0.6	15.73(8)	20.94(4)	8.55(29)	0.6				
15.17(8)	20.39(5)	6.70(29)	0.7	15.25(9)	20.56(4)		0.6				
16.85(9)	21.55(5)	9.03(2)	0.8	15.94(10)	20.80(7)	6.94(7)	0.5	14.94(13)	20.11(7)	6.42(15)	0.6
16.73(12)	21.57(6)	8.67(26)	0.9	16.14(9)	20.99(6)	7.17(7)	0.6	15.10(10)	20.17(6)	6.56(12)	0.6
14.37(15)	19.96(12)	6.49(34)	1	12.56(4)			0.3				
13.44(10)	18.98(15)		0.9	12.54(10)	18.58(26)		0.6				
12.79(15)	19.03(10)		1	12.96(18)	18.66(14)	4.17(1.83)	1				
12.21(13)			2	12.57(10)	18.35(18)	4.00(1.31)	1				
15.27(7)	19.80(7)	6.56(12)	1	14.38(7)	19.31(11)	4.97(6)	0.7	13.42(10)	18.99(6)	4.46(10)	1
14.84(7)	19.31(10)	5.81(11)	2	14.51(5)	19.59(6)	4.71(5)	0.6	13.21(11)	19.00(7)	4.57(10)	1

For this reason Sigel proposed another equation [11] to be used for the same purposes:

$$CuA + CuB \overset{K^1_{MAB}}{\rightleftharpoons} CuAB + Cu \qquad (2)$$

i.e. he compared the formation of a heteroligand complex with that of two initial mono-complexes. The theoretical value is K^1_{MAB} = I(log K^1_{MAB} = 0)*, but the compounds in the right- and left-hand parts of eqn. 2 are very different in their chemical nature, and therefore the deviation of K^1_{MAB} value from the statistical one does not yield to simple interpretation. Here, solvation, electrostatic, steric and other factors are involved.

Since we failed to find any better alternative to eqn. 2 in the literature we calculated the values for both K^1_{MAB} and K^2_{MAB}. These values are given in Table II.

The change in K^1_{MAB} and K^2_{MAB} is generally symbatic, excluding two cases. Moreover, it is in agreement with the changes in the complex stability constants: maximal K^1_{MAB} and K^2_{MAB} values correspond to the heteroligand complexes of maximum stability. Thus, the tendency of a pair of homoligand complexes to form heteroligand structure does not alter monotonically with the increase in steric interactions, but passes through the maximum. In different combinations of amino acids this maximum corresponds to different combination of substituents introduced into the amino groups, which clearly indicates that steric interactions depend not only on the N-alkyl substituents but also on the type and arrangement of substituents at α-carbon atoms. The latter statement is confirmed primarily by the fact that both K^1_{MAB} and K^2_{MAB} (apart from all the above-considered factors) also depend on the optical configuration of the complex-forming ligands.

*Considering the difference in the probability of formation of binary and ternary complexes Sigel chose log K^1 = −0.9 [11].

TABLE II. Disproportionation Constants for Heteroligand Complexes of Copper(II).

Amino acid		S-Pro		S-Hyp		S-Hyp		S-BzlPro		S-BzlHyp		S-BzlaHyp	
		$\log K^2$ [a]	$\log K^1$ [b]	$\log K^2$	$\log K^1$	$\log K^2$	$\log K^1$	$\log K^2$	$\log K^1$	$\log K^2$	$\log K^1$	$\log K^2$	$\log K^1$
Val	*S*	0.11	−1.19	1.77	0.10	2.07	−0.10	1.51	−0.40	4.52	1.08	3.03	0.45
	R	0.29	−0.99	0.61	−0.48	1.49	−0.39	0.07	−1.12	4.24	0.94	4.05	0.91
MeVal	*S*	3.39	0.25			4.67	1.17					3.75	0.78
	R	3.39	0.25			4.27	0.97					4.15	0.98
BzVal	*S*	4.30	1.18	4.42	1.59	5.88	1.94	4.58	1.31	2.69	0.33	5.22	1.71
	R	4.14	1.10	4.18	1.47	4.78	1.85	2.72	0.37	1.53	−0.25	4.36	1.28
Me_2Val	*S*	4.80	2.24	6.20	2.29	4.96	1.32	1.86	−0.25	3.93	0.76	4.34	1.08
	R	0.86	−0.73	5.24	1.81	5.36	1.52	1.84	−0.27	3.15	0.37	4.60	1.21
Bzl,MeVal	*S*		−0.48				1.63						1.43
	R		0.58				1.79						1.22

[a] $\log K^2 = 2 \log \beta_{MAB} - \log \beta_{MA_2} - \log \beta_{MB}$. [b] $\log K^1 = \log \beta_{MAB} - \log \beta_{MA} - \log \beta_{MB}$.

III. Enantioselectivity of Heteroligand Complex Formation

Different values of K^1_{MAB} and K^2_{MAB} found for the systems of complexes containing diastereometric ligand sets show that these systems are characterized by enantioselective effects. The effects are also clearly seen from the comparison between the stability constants for the corresponding diastereometric heteroligand complexes. The differences in stability given in Table III do not exhibit such a simple correlation with the degree of ligand steric overload as that observed for the stability constants. Thus, heteroligand proline complexes display no enantioselectivity, if the other partner is represented by valine or its monosubstituted derivatives. For N,N-dimethylvaline the *SS*-structure is more stable, while the *RS*-structure is more stable for N-benzyl-N-methylvaline. A different picture is observed for the complexes of allo-hydroxyproline, where enantioselectivity is displayed only for the complexes with valine or N-methylvaline and is lacking for the rest of the derivatives (Table III). The N-benzyl substituent introduced into the heterocyclic ligand gives rise to enantioselectivity primarily in heteroligand complexes with N-benzylvaline, and to sign inversion of the enantioselectivity for allo-hydroxyproline series.

The changes in the value and sign of enantioselectivity, when passing from one system to another, are due to the intricate mechanism of this effect. In the whole series of our studies steric interligand interactions were identified as being one of the main reasons for enantioselectivity [6, 7]. From this viewpoint the structure where the distances between all the alkyl substituents are maximum will be most preferable. Usually this structure corresponds to the complexes which contain two ligands belonging to opposite configurational series. On the other hand, Sekiya demonstrated an important stabilizing role of hydrophobic interactions within the complexes [12], and from these standpoints the structure containing the ligands of the same chirality should be most advantageous. The situation becomes much more difficult for the ligands with N-alkyl substituents: in this case it is not easy to say which of the structures would correspond to the maximum of

TABLE III. Enantioselectivity Effects in Formation of Heteroligand Amino Acid Copper(II) Complexes.

Amino acid	Val		MeVal		BzlVal		Me_2Val		Bzl, MeVal	
	$\Delta \log \beta$	$\delta(\Delta G)$[a]	$\Delta \log \beta$	$\delta(\Delta G)$	$\Delta \log \beta$	$\delta(\Delta G)$	$\Delta \log \beta$	$\delta(\Delta G)$	$\Delta \log \beta$	$\delta(\Delta G)$
Pro	[b]	[b]	[b]	[b]	[b]	[b]	−2.97	−16.92	0.99	5.64
Hyp	−0.58	−3.31			[b]	[b]	−0.48	−2.74		
aHyp	−0.29	−1.65	−0.20	−1.14	[b]	[b]	[b]	[b]	[b]	[b]
BzlPro	[b]	[b]			−0.93	−5.30	[b]	[b]		
BzlHyp	−0.14	−0.80			−0.58	−3.31	[b]	[b]		
BzlaHyp	0.51	3.10	0.20	1.10	−0.43	−2.40	[b]	[b]	[b]	[b]

[a] $\delta(\Delta G) = 2,3RT \log \frac{\beta_{RS}}{\beta_{SS}}$ (kJ/mol) [b] Absence of enantioselectivity.

hydrophobic interactions and minimum of repulsive steric interactions between the substituents.

If we take into account the ligands in axial positions of the copper atom and the solvation shell of the complexes, the forecasting of enantioselectivity is effectively impossible, and any of these factors can prove to be decisive. Additional studies with the use of several physico-chemical methods could give a complete picture of the mechanisms of enantioselectivity in any specific system.

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