Dependence of the Co-ordination Sphere in Bis(valinato)-copper(II) Complexes on Solvent and Alkylation at Nitrogen

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The ^{14}N superhyperfine structure in the ESR spectra of bis(amino acidato)copper(II) complexes (valine, alanine and their *N,N*-diethylated counterparts) was studied as a function of the solvent composition and temperature. The equilibrium between two components, presumably the *cis* and *trans* isomers, was found to depend on the solvent dioxane:D_2O ratio and on temperature, in different ways for the valine and alanine complexes. Thus addition of dioxane to water solvent, and an increase in temperature from 293 K, stabilizes the valine complexes and destabilizes the alaninate complexes. This suggests a ligand–ligand interaction between the two isopropyl residues of the valinate.

Many of the specific biologically relevant interactions are achieved by the side-chain groups of amino acids in proteins. Such interactions may also be important in the low-molecular-weight species. There is little knowledge of aliphatic–aliphatic side-chain interactions in metal-ion complexes,[1–3] and the influence of organic solvents on these interactions has hardly been studied. It was suggested recently[2,3] that ligand–ligand interaction is reflected in the stability of copper(II) complexes.

Electron spin resonance spectroscopy has been used extensively for the characterization of copper(II) complexes,[4–6] and provided information on the nature of the co-ordination sphere in species predominating in different pH regions.[7] For a number of bis(amino acidato)copper(II) complexes in aqueous solution the presence of two components, presumably *cis* and *trans* isomers, was confirmed by the ^{14}N superhyperfine structure in the ESR spectra.[7]

For the valine complex of Cu^{II} it was proposed that its increased stability compared with the alanine complex was due to the hydrophobic contacts of the two valine isopropyl residues.[2] These residues can come into contact with each other only in a *trans* arrangement of the glycinate-like units in the equatorial part of the co-ordination sphere.

The increased stability of the bis(valine) complex as compared to the bis(alanine) complex in D_2O–dioxane solvent is accompanied in the former by a shift of the *cis–trans* equilibrium towards the *trans* isomer. This shift can be detected by the ^{14}N superhyperfine structure in the ESR spectra of these complexes. In this context we have studied the ESR spectra of bis(valinato)-, bis(alaninato)-, bis(*N,N*-diethylvalinato)- and bis(*N,N*-diethylalaninato)-copper(II) complexes.

Experimental

Preparation of the Ligands and the Copper(II) *complexes.*—The amino acids (L-valine and L-alanine) used for the preparation of the copper(II) complexes were of analytical grade purity. The complexes of the non-alkylated amino acids were prepared from the amino acids and copper(II) hydroxide using the method described by Yasui.[8] The *N,N*-dialkylated ligands were synthesised by ethylation of the corresponding amino acids through condensation with acetaldehyde and subsequent hydrogenation over 5% Pd on activated charcoal.[9] The products isolated were purified by repeated recrystallization from MeOH–Me_2O, and their identity confirmed by elemental analysis, IR, ^{1}H NMR and mass spectra.

Copper(II) complexes of alkylated amino acids were prepared by refluxing copper(II) acetate monohydrate with the sodium salt of the ligand in anhydrous methylene chloride for 3 d under anhydrous conditions. Crystalline complexes were obtained by removing sodium acetate and slowly evaporating the red-violet CH_2Cl_2 solution *in vacuo*.[10]

Spectroscopy.—The UV/VIS spectra were measured by means of a Hewlett-Packard (HP-8452) diode-array spectrometer over the range 190–800 nm in steps of 2 nm. Sample solutions contained complex concentrations of 1–10 mmol dm^{-3}.

The ESR spectra were taken using a Varian E-12 Century Line Series spectrometer equipped with a Bruker variable-temperature control unit. The temperature was varied from 274 to 330 K. The *g* factor was measured relative to diphenylpicrylhydrazyl (dpph) as a standard ($g = 2.0036 \pm 0.0003$).[11]

The ESR spectra of bis(amino acidato)copper(II) complexes consist of four ($2I + 1$) resonances, arising from the hyperfine coupling of an unpaired electron with a copper nuclear spin, $I = \frac{3}{2}$.[7] The two isotopes ^{63}Cu (69%) and ^{65}Cu (31%) have slightly different magnetic moments. The *g* values corresponding to the two components were found to be similar, whereas there were differences between the copper hyperfine splitting constants.[12] Each of these two complexes has two nitrogen atoms with spin $I = 1$, and two oxygen atoms in the equatorial part of the co-ordination sphere, which can give rise to ^{14}N superhyperfine structure. The resolution of the ^{14}N superhyperfine lines is enhanced in a second-derivative presentation (Fig. 1). The high-field line ($m = \frac{3}{2}$) is characterized by an asymmetric septet [Fig. 1, spectrum (*a*) for the alanine and (*b*) for the valine complex]. The ^{14}N superhyperfine structure of such spectra was interpreted in terms of two overlapping quintets, each with an intensity ratio 1:2:3:2:1, arising from the two N-donor atom sets of the *cis* and *trans* isomers in equilibrium.[7] The quintet at higher field was assigned to the *trans* isomer.[12,13]

Results and Discussion

Sigel and co-workers[2] have proposed that in dioxane–water solution the increased stability of the bis(valinato)- as compared with the bis(alaninato)-copper(II) complex is due to the hydrophobic contacts of the two isopropyl residues of the former. If this hypothesis is correct the addition of dioxane to an aqueous solution of this complex should be followed by a shift in the *cis–trans* equilibrium towards the *trans* isomer, because the

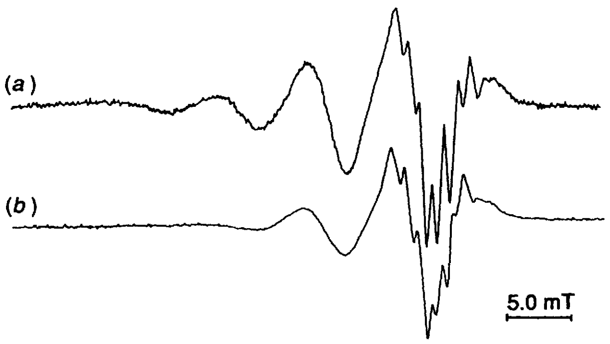

Fig. 1 Second-derivative ESR spectra of bis(alaninato)copper(II) (*a*) and bis(valinato)copper(II) (*b*) at 277 K

Table 1 The ESR and visible absorption parameters for bis(amino acidato)copper(II) complexes in two different solvents

	λ_{max}[b]	g_0		a_{Cu}/mT		a_N/mT		*cis–trans* Equilibrium	
Ligand[a]	/nm	*c*	*b*	*c*	*b*	*c*	*b*	*c*	*b*
AlaO	612	2.123	—	6.85	—	1.0	—	Yes	—
ValO	612	2.126	2.124	7.00	7.60	1.0	1.0	Yes	*trans*
deala	656	2.107	2.104	8.60	9.00	1.0	1.1	*trans*	*trans*
deval	656	2.109	2.106	8.20	9.00	1.0	1.0	*trans*	*trans*

[a] AlaO = Alaninate, ValO = valinate, deala = *N,N*-diethylalaninate, deval = *N,N*-diethylvalinate. [b] In dioxane–D_2O (1:1). [c] In D_2O.

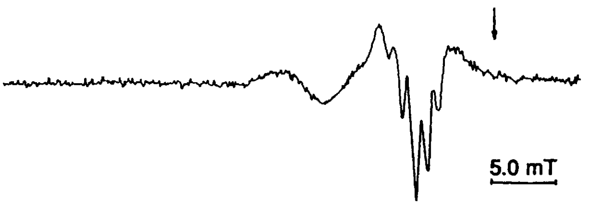

Fig. 2 Second-derivative ESR spectrum of bis(valinato)copper(II) in 50% dioxane–D_2O at 277 K

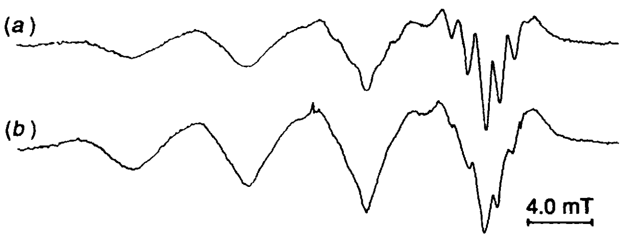

Fig. 3 Second-derivative ESR spectra of bis(*N,N*-diethylalaninato)copper(II) in 50% dioxane–D_2O at 276 (*a*) and 296 K (*b*)

Table 2 The ESR and visible absorption parameters for bis(valinato)copper(II) as a function of the % dioxane in dioxane–D_2O solvent

Dioxane (%)	g_0	a_{Cu}/mT	a_N/mT	*cis–trans* Equilibrium	λ_{max}/nm
0	2.123	7.0	1.0	Yes	612
10	2.126	7.0	1.0	Yes	650
25	2.126	7.2	1.0	Yes	680
36	2.121	7.1	1.0	*trans*	—
50	2.124	7.6	1.0	*trans*	662
90	2.123	7.9	1.0	*trans*	624

two isopropyl residues can come into contact only in the *trans* arrangement.

The ESR parameters for both valine and alanine complexes are shown in Table 1. They are in accord with literature data for the natural abundance of copper isotopes,[7] confirming the presence of predominantly $[CuL_2]^{2+}$ complexes in solution.[7]

For both complexes of valine [Fig. 1(*b*)] and alanine [Fig. 1(*a*)] the best resolution of the ^{14}N superhyperfine lines was obtained in the temperature range 274–278 K. Above 293 K the superhyperfine lines were lost completely. This is obviously due to the temperature-dependent inverconversion between the *cis* and *trans* isomers, which at above 293 K is too rapid with respect to the ESR time-scale.

Fig. 2 shows the ESR spectrum (second derivative) of bis(valinato)copper(II) in 50% water–dioxane solution. The five ^{14}N superhyperfine lines with an intensity ratio 1:2:3:2:1 suggest that the *trans* isomer is the predominant species. The resolution of the ^{14}N superhyperfine lines increased with increasing temperature up to 300 K in a dioxane–D_2O mixture, while in pure D_2O it could not be detected above 293 K. This suggests an increase in stability of the *trans*-valine isomer in D_2O–dioxane.

The bis(alaninato)copper(II) complex is not stable even in 10% dioxane–water, and therefore ESR spectra could not be obtained.

The similar g_0 and a_0(Cu) values for the alanine and valine complexes in Table 1 suggest similar types of bonding in the two cases. A small decrease in g_0 and an increase in a_0(Cu) for the valine complex in 50% D_2O–dioxane cannot explain the increased stability of this complex.

In the alanine complex the two CH_3 groups cannot come into hydrophobic contact (van der Waals interaction) in the water–dioxane mixture. In contrast the interaction of the two isopropyl residues was observed for the *N,N*-dimethylated valine complex in the crystal structure.[14] Thus it can be expected that dioxane favours such an interaction that adds to the stability of the valine complex in comparison to the alanine complex. The shift to the *trans* conformer in D_2O–dioxane solvent and its stability even at 300 K corroborates this.

In Table 2 the ESR parameters of the bis(valinato)copper(II) complex are shown as a function of the increasing dioxane:water ratio. The seven superhyperfine lines due to the *cis–trans* isomers in equilibrium can be observed with up to 30% dioxane in water. At higher dioxane:D_2O ratio only five lines with an intensity ratio of 1:2:3:2:1 for the *trans* isomers were observed at all the temperatures examined.

The ^{14}N superhyperfine structure of the ESR spectra of bis(glycinato)-like copper(II) complexes was also studied. Fig. 3 shows the ESR spectra of the bis(*N,N*-diethylalaninato)copper(II) complex dissolved in 50% dioxane–water. The five ^{14}N superhyperfine lines, presumably of the *trans* isomer, are well resolved at 276 K [spectrum (*a*)]. At the higher temperature (above 296 K) the lines are broadened [spectrum (*b*) was taken at 296 K]. On the other hand, in pure D_2O solvent the five ^{14}N superhyperfine lines of the *trans* isomer are well resolved up to 316 K. These results suggest that although alkylation of the N atoms of alanine favours the *trans* isomer, the ethylated complex is destabilized in the presence of dioxane.

The opposite result was obtained for bis(*N,N*-diethylvalinato)copper(II). Fig. 4 shows the ESR spectra of this complex in dioxane–D_2O. The ^{14}N superhyperfine lines at 296 K [spectrum (*b*)] are better resolved than at 276 K [spectrum (*a*)], contrary to the results obtained for the bis(*N,N*-diethylalaninato) complex (Fig. 3) under similar conditions.

The five ^{14}N superhyperfine lines in the spectra of the bis(*N,N*-diethylvalinato) complex suggest that the ethylation of the nitrogen atoms of valine makes the *trans* co-ordination of Cu^{II} the dominant species in pure D_2O and in dioxane–water solution. The ^{14}N superhyperfine lines are better resolved (sharper) in dioxane–water than in pure D_2O even at 316 K.

These results can be explained by the stabilization of the

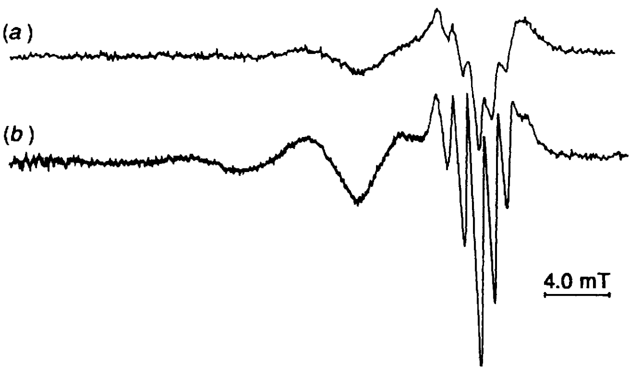

Fig. 4 Second-derivative ESR spectra of bis(*N*,*N*-diethylvalinato)-copper(II) in 50% dioxane–D_2O at 276 (*a*) and 296 K (*b*)

bis(*N*,*N*-diethylvalinato) complex and destabilization of the bis(*N*,*N*-diethylalaninato) complex in dioxane–water solution. As the N_2O_2 donor-atom set bound to copper(II) is identical in both the alanine and valine complexes, the resolution of the ^{14}N superhyperfine lines in the ESR spectra of the latter complex has to be related to the hydrophobic interaction between the aliphatic side chains.

Conclusion

The ^{14}N superhyperfine structure of the ESR spectra of bis(valinato)copper(II) suggests that in dioxane–water solution (> 30% dioxane) the *trans* isomer is the predominant species, *i.e.* the addition of dioxane induces a shift in the *cis–trans* equilibrium towards the *trans* isomer. The *trans* isomer of the valine complex is stable even at 316 K.

The ESR spectra of both the *N*,*N*-dialkylated alanine and valine complexes of Cu^{II} show that only the *trans* isomers occur in D_2O and in dioxane–D_2O solvents, in accord with crystallographic data reported recently for bis(L-*N*,*N*-dimethylvalinato)copper(II)[14] and bis(L-*N*,*N*-diethylalaninato) copper(II).[15,16]

From the temperature dependence of the ESR spectra of both alkylated complexes we deduce that in dioxane–D_2O the *trans* isomer of the bis(*N*,*N*-diethylvalinato)copper(II) complex is stable up to 320 K, while the *trans* isomer of the bis(*N*,*N*-diethylalaninato)copper(II) complex is stable only in the range 276–296 K. The increased stability of the valine complex, reflected in the ^{14}N superhyperfine structure of the ESR spectra reported, can be attributed only to the ligand–ligand interaction between the valine aliphatic side chains.

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