Cadmium(II) Complex with L-Carnosine as a Ligand and the Tautomeric Change of the Imidazole Moiety upon Complexation†

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L-Carnosine functions as a quadridentate ligand in a novel cadmium(II) complex in which the imidazole moiety of the ligand undergoes tautomeric change during complex formation; the process has been characterised by infrared and ^{13}C NMR spectroscopy.

L-Carnosine (*β*-alanyl-L-histidine) (**1**) is used in the treatment of surgical wounds, gastric ulcers, arthritis, inflammations and diseases caused by active oxygen.[1] The interactions of this ligand with bivalent zinc, both in solution[2] and in the solid state,[3] have been reported. L-Carnosine acts as a bridging dianionic ligand following removal of the amide and carbonyl protons in its copper(II) complex.[4] The ligand coordinates to one copper centre through its three donor atoms, namely the oxygen of the carboxylate group, the nitrogen of the NH_2 group and another nitrogen of the deprotonated amide group. The same ligand binds the other copper centre through N(1) of the imidazole moiety. Cadmium occupies an interesting position in the periodic table, being placed in group 12 between zinc and mercury, both of which play essential roles in several biological processes.[5,6] It is thus interesting to study the interaction of cadmium(II) ion with L-carnosine. In this paper we report our preliminary findings on the isolation and characterisation of a novel complex of cadmium(II) with L-carnosine. We propose the formulation for the isolated complex as $CdL\cdot H_2O$, where H_2L = L-carnosine.

The TGA curve of the complex shows a loss of weight at around 130 °C and the gradual decomposition continues up to 350 °C without the formation of any stable intermediate.

The decrease in the IR absorption frequency of the amide carbonyl band in the complex (1620 cm^{-1}) by 36 cm^{-1} compared with the free ligand value (1656 cm^{-1}) indicates the loss of hydrogen from the amide nitrogen[7] followed by the coordination to cadmium(II). Similar behaviour of the amide carbonyl frequency is also reported[8] in zinc(II) complexes with glycil-L-histidine and L-alanyl-L-histidine. Both symmetric and asymmetric stretching vibrations of the carboxyl group (1408 and 1582 cm^{-1}, respectively) also shift to lower frequencies in the complex indicating coordination through the carboxylate oxygen of the ligand. The strong band (3250 cm^{-1}) in the complex suggests coordination through the nitrogen of the primary amine group of the ligand. This band disappears in the deuterated complex. Thus the qualitative interpretation of the IR spectral data suggests that L-carnosine is coordinated to cadmium(II) through its three donor atoms, namely, the oxygen of the carboxylate group and two nitrogen atoms, one from the primary amine and the other from the deprotonated amide group. We could not get any information from the IR spectrum regarding the coordination through the ring nitrogen of the imidazole moiety which is also a potential donor atom.

Table 1 shows the ^{13}C NMR spectra of L-carnosine (**1**) and the prepared cadmium(II) complex. The signals of L-carnosine are assigned as reported in the literature.[9] The imidazole moiety of L-carnosine exists in the N(3)—H tautomeric form in the solid state.[10] The C(2) and C(5) chemical shifts for L-carnosine overlap at 135.7 ppm but split into 148.9 and 135.3 ppm respectively for its cadmium(II) complex **2**. The C(2) and C(5) signals in the complex show downfield shifts of 13.2 and 12.5 ppm respectively to that of the free ligand L-carnosine suggesting a drastic ligand change upon complexation. The ^{13}C NMR spectra of imidazole **3** L-histidine **4**, cyclo-L-methionine-L-histidine **5** and their respective zinc(II) complexes [**6–8**, respectively] are also recorded and presented in Table 1. The imidazole moiety exists in the N(3)—H form[11] in the free ligand. The chemical shifts for imidazole and its zinc(II) complex **6** remain almost unaffected for the C(2) and C(5) atoms (0.9 ppm downfield and 1.2 ppm upfield respectively). The resonance signal of the complex **6** shifts downfield by 4.1 ppm compared to free imidazole for the C(4) atom. Again the C(2) and C(5) signals for the zinc(II) complex of L-histidine **7** also do not change appreciably (0.6 upfield and 1.0 ppm downfield) as compared with L-histidine. The C(4) signal in the complex **7** shows a downfield shift (1.5 ppm) compared with L-histidine. The imidazole moiety exists in its N(3)—H tautomeric form[12] in both the complexes of zinc(II) with imidazole and L-histidine and N(1) coordinates to zinc(II).[13] The C(2) and C(5) signals in the zinc(II) complex of cyclo-L-methionine-L-histidine **8** shift to 4.2 ppm downfield and 6.8 ppm upfield with respect to the free ligand **5**. Also the C(4) signal shifts downfield by 4.8 ppm. These changes for the above complex **8** with respect to the free ligand **5** are in the same direction as in the case of the prepared cadmium(II) complex of L-carnosine, in comparison with the free ligand. The imidazole moiety exists in the

Table 1 ^{13}C NMR data for **1–8**

	δ_C					
Compound	CO_2	N(H)CO	C(2)	C(5)	C(4)	C(α′)
1	177.9	169.1	135.7	135.7	115.1	33.8
2	176.9	172.0	148.9	135.3	127.6	38.3
3			136.3	126.8	115.3	
6			137.2	125.6	119.4	
4	175.7		137.4	135.8	113.8	
7	178.0		136.8	136.8	115.3	
5		170.0	134.9	134.9	119.1	52.9
8		167.9	139.1	128.1	123.9	54.8

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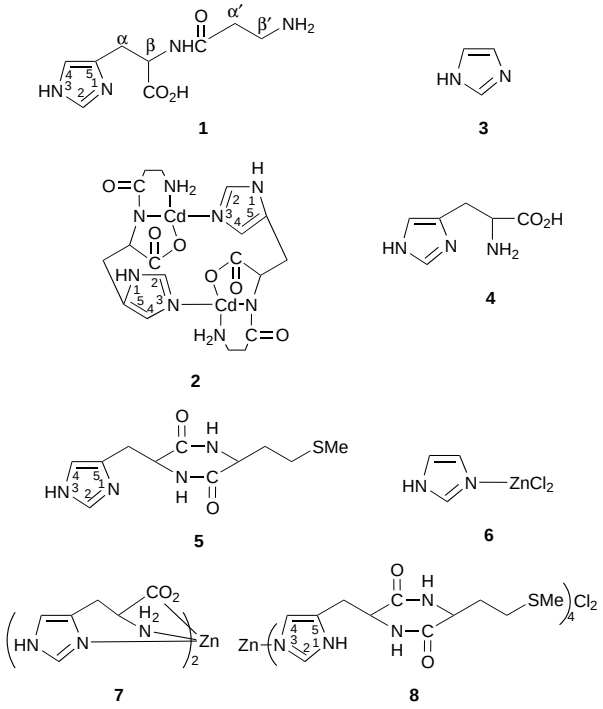

Fig. 1 L-Carnosine **1**, other histidine derivatives and their complexes

N(3)—H form in cyclo-L-methionine-L-histidine[11] but, in its complex with zinc(II), the imidazole moiety exists in the N(1)—H form in the solid state.[14] Hence on the basis of the above discussions we can conclude that in the prepared cadmium(II) complex of L-carnosine, the imidazole moiety is present in its N(1)—H form showing the change of the tautomeric form on complexation. Our conclusion is also consistent with the observations of Friedlich and Wasylishen[9] who recorded the ^{13}C NMR spectra of various histidine derivatives. The ring nitrogen at N(3) will coordinate to cadmium(II). Simultaneous binding of all the four donor atoms of the ligand to the same Cd^{II} centre will not be feasible due to severe ring strain by the coordination of the ring nitrogen at N(3). Hence we propose that the ligand acts as a bridge between two Cd^{II} centres as shown in compound **2**. The signals for the amide carbonyl and the α′-carbon in the cadmium(II) complex (Table 1) shift downfield by 2.9 and 4.5 ppm respectively with respect to L-carnosine indicating the participation of the amide group in the coordination.

Experimental

^{13}C-CP/MAS NMR spectra were recorded in the solid state on JEOL GSX 400NB spectrometer with Me_4Si as internal standard. IR spectra were recorded on a PE983 spectrophotometer. Thermogravimetric analysis was carried out with a Derivatograph (System: F. Paulik, J. Paulik and L. Erdey, MOM, Budapest). The finely powdered substances were heated at the rate of 2 °C per minute. L-Carnosine and other histidine derivatives were from Sigma, USA. Other chemicals used were of analytical grade.

The cadmium complex of L-carnosine was prepared by adding a saturated aqueous solution of $CdCl_2 \cdot 2.5H_2O$ (2.28 g, 10 mmol) to a solution of L-carnosine (2.26 g, 10 mmol). The pH of the L-carnosine solution was maintained at ca. pH 7.5 by adding dilute NaOH. The resultant clear solution was stirred and the pH fell below 7.0. The volume of the solution was reduced to one third by heating over a water bath. On cooling white crystals gradually appeared. The yield was 38%. The zinc(II) complexes of imidazole,[15] L-histidine[13] and cyclo-L-methionine-L-histidine[14] were prepared by earlier methods as reported in the literature. The cadmium content was estimated gravimetrically as molybdate after decomposing the complex in a platinum crucible at 800 °C with HNO_3 and finally with H_2SO_4. (Found: Cd, 32.35; C, 31.02; H, 3.67; N, 16.28. Cd $(C_9H_{12}N_4O_3)\cdot H_2O$ requires Cd 31.71; C, 30.47; H, 3.95; N, 15.80%). The analytical data of the zinc(II) complexes are within 1% of reported data.[13–15]

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