New Investigations on Copper(II) Sebacate,
A Potentially Useful Drug for Copper Supplementation

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SUMMARY. We have recently improved the synthesis of copper(II) sebacate, a promising drug for copper-supplementation, and investigated some of its general physicochemical properties. In this paper we present a through analysis of its infrared spectrum, complemented by a comparison with those of free sebacic acid and disodium sebacate. Some solubility tests as well as a lipophilicity assay, which may be useful in the design of an adequate delivery system for the drug, are also reported.

RESUMEN. "Nuevas Investigaciones Sobre Sebacato de Cobre(II), una Droga Potencialmente Util para la Suplementación de Cobre". Recientemente hemos mejorado la técnica de síntesis del sebacato de cobre(II), una droga muy promisoria para la suplementación de cobre, e investigado sus propiedades fisicoquímicas generales. En este trabajo presentamos un análisis pormenorizado de su espectro de infrarrojo, complementado con una comparación de los correspondientes al ácido sebácico libre y al sebacato disódico. Asimismo, se reportan algunos ensayos de solubilidad y un estudio de lipofilicidad, los que pueden ser útiles para diseñar un sistema adecuado para dispensar la droga.

Menkes disease is an inherited disorder associated with anomalies in the copper metabolism, and is probably related with an insufficient absorption of this element [1-3].

Different attempts have been made to correct the abnormalities related to this disease with copper administration, in the form of different chemical compounds and complexes [4-6]. On the other hand, supplementation of copper has also become an important problem in veterinary medicine (cf. for example Smart *et al.* [7] and references therein).

Some not well defined copper compounds; in the presence of sebacic acid (decanedioic acid), has claimed to be useful in this context [5,8]. As sebacic acid appears as a very interesting ligand for the supplementation of essential trace metals, due to its general chemical properties which probably facilitate the mobiliza-

tion of metals through lipidic membranes and similar biological barriers, we initiated some work to isolate and characterize well defined copper complexes of this acid.

In a previous paper, we described a method for the facile synthesis of very pure copper(II) sebacate samples, and a structural proposal for the complex could also be advanced [9].

As infrared spectroscopy is a very useful tool for the rapid characterization of this compound, we present now a detailed analysis of this spectrum and, in order to facilitate the assignments, the spectra of the free acid and of its disodium salt were also recorded and discussed.

The present paper is completed with some solubility tests and a standard lipophilicity assay in order to find adequate ways for the delivery of the drug.

EXPERIMENTAL

The complex was prepared by treating disodium sebacate with copper(II) sulfate, following the detailed procedure described in the previous paper [9].

The infrared spectra were recorded with a Perkin Elmer 580 spectrophotometer, using the KBr pellet technique.

The lipophilicity test was made by determining the water/n-octanol partition coefficient [10] and working as previously described [11].

RESULTS AND DISCUSSION

Infrared spectrum

As stated above, and in order to facilitate the spectroscopic analysis, the spectrum of the complex was compared with those of the free solid acid and of disodium sebacate.

The spectra in the high frequency region are shown in Figure 1, whereas the region between 1800 and 300 cm^{-1} is shown in Figure 2. The measured band positions together with the assignment proposed for the copper complex are given in Table 1.

To facilitate the assignment, the discussion of the spectra will be ordered on the basis of the most characteristic vibrations.

C—H and O—H modes

The ν (OH) stretching mode of the free acid appears as a broad band centered at 3025 cm^{-1}, whereas a number of weak bands located between 2800 and 2500 cm^{-1} are assigned, as usually, to overtone and combination modes [12]

The symmetric and antisymmetric CH$_2$ stretching vibrations are found in practically the same range in the free acid and in the two investigated compounds. In the case of disodium sebacate this region appears specially well resolved and also a band located at 2886 cm^{-1}, absent in the other two cases, can be clearly identified.

The broad and strong band found at 934 cm^{-1} in the acid is assigned to the characteristic out of plane OH⋯O wagging mode of the carboxylic acid dimer [12,13]
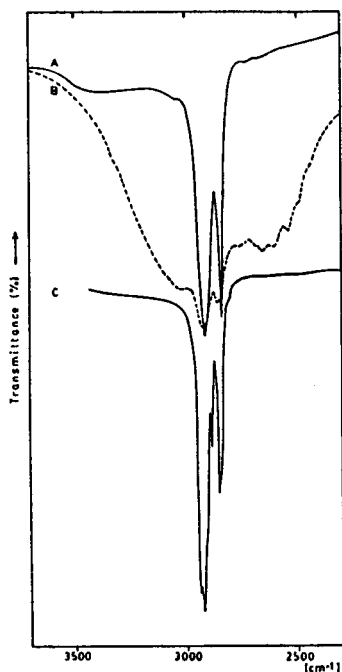
Figure 1. Infrared spectra between 3500 and 2500 cm^{-1} of copper(II) sebacate (A), sebacic acid (B) and disodium sebacate (C).
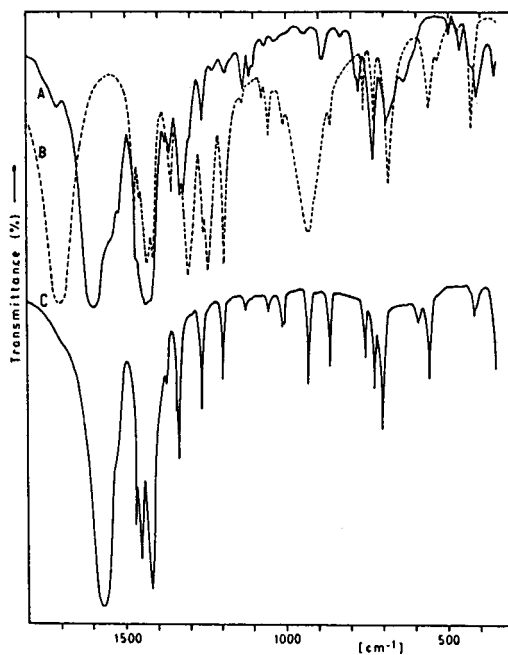
Figure 2. Infrared spectra between 2800 and 300 cm^{-1} of copper(II) sebacate (A), sebacic acid (B) and disodium sebacate (C).

Typical skeletal modes of the aliphatic chains are expected to lie between 1100 and 1300 cm^{-1} and around 720-730 cm^{-1}, in the same range as some other vibrations which will be discussed in the next section.

Usually, long chain saturated carboxylic acids and their salts present a regulary spaced progression of weak sharp IR bands between 1345 and 1180 cm^{-1}, assigned to the various interacting CH$_2$-wagging vibrations in the (CH$_2$)$_n$ part of the chain [12]. The number of bands can be related to the number of carbons in the chain: for an acid with an even number (N) of carbon atoms in the chain, the number of expected bands is N/2 [14]. These bands have been clearly identified in the copper complex, whereas in the free acid they are partially overlapped by other bands and in the disodium salt only two of the four expected bands could be identified.

Carboxylate and related bands

In the free acid, the strong IR band centred át 1702 cm^{-1} can be assigned with certainty to the C=O stretching mode. The group of bands between 1400-1800 cm^{-1} involves CH$_2$-skeletal modes as well as the COH- in plane bending vibration, whereas the multiplet between 1200 and 1300 cm^{-1} originates in a superposition of other CH$_2$-skeletal modes (involving also the above mentioned CH$_2$-progression) and the stretching mode of the C-O bond of the C-OH group [12,13].

In the case of disodium sebacate, the C=O and C-O bonds become nearly equivalent and the two stretching vibrations run together in the spectrum. The v_{as}

Acid	Disodium-salt	Cu(II)-complex	Assignm. for Cu(II)-complex
3025	-	-	
2935/2915	2939/2925	2938sh/2922	ν_{as} (CH$_2$)
-	2866	-	
2870/2850	2854/2843	2848	ν_s (CH$_2$)
2760			
2705			
2662			
2611			
2545			
1702	1563	1598	ν_{as} (COO$^-$)
-	-	~1550/1520	
1472/1458	1462	~1470 sh	(CH$_2$)sciss.
1435/1417	1447/1417	1443/1420 sh	ν_s (COO$^-$)
1358	1368	1376/1361 ⎫	
1333	1338/1330	1337 ⎬	(CH$_2$)deform.
1308	-	1320 ⎭	
~ 1285 sh	-	~1300 sh ⎫	
1260	1261	1262	
1246	-	- ⎬	(CH$_2$)wagg.
-	-	1228	(progression)
1195	1191	1189 ⎭	
1133	-	1133 ⎫	
-	1115	1112	
-	-	1100 ⎬	(CC) stretch.
1072	-	1062	
1055	1045	1033 ⎭	
1010	1002/995	-	
934	-	-	
-	922	890	
863	855	835	
762	746	787 sh /779	
732	715	731	(CH$_2$) rock.
687	692	692/688 sh	δ (COO-)
-	-	634	ν (Cu-O) (?)
-	579	-	
559	-	-	
545	547	-	
-	-	495	
470	-	460	
428	-	430 sh ⎫	
-	404	410/395 sh ⎭	δ (COO$^-$)
-	-	359	ν (Cu-O) (?)
338	340	322	

sh = shoulder

Table 1. Infrared spectra of sebacic acid, disodium sebacate and copper(II) sebacate (band positions in cm^{-1}).

(COO⁻) mode is found at 1536 cm⁻¹ and the corresponding symmetric stretching at 1417 cm⁻¹. Near to the latter, two skeletal modes, probably CH_2-scissoring vibrations [12] can be clearly identified at 1462 and 1447 cm⁻¹, whereas the region between 1200-1300 cm⁻¹ appears greatly simplified.

In the copper(II) complex, a similar effect can be observed. The antisymmetric (COO⁻) mode is found as a broad and somewhat deformed band at 1598 cm⁻¹ and the corresponding symmetric one is centered at 1433 cm⁻¹.

The position of these two carboxylate bands was of great importance for the structural characterization of the complex [9]. As the two ν(COO⁻) stretching lie close to the free ion values (cf. Table 1) and the frequency difference between these two modes is of 165 cm⁻¹, it becomes evident that the carboxylate group act as bridging ligands [15]. Therefore, a dimeric structure containing Cu-Cu moieties, bridged by carboxylate groups, similar to that found in the well known copper(II) acetate and other Cu(II) complexes of carboxylic acids [16-18], has been proposed [9] and this proposal is also supported by the magnetic behaviour and the electronic spectra of copper(II) sebacate [9].

In the spectral range below 900 cm⁻¹ the assignment is more complicated. Additional bending modes of the aliphatic chain are expected to appear [12] and one characteristic CH_2-rocking mode could be identified.

Two δ(COO⁻) modes were assigned by comparison with values found in other similar complexes [15] and in the recently reported spectrum of bis (imidazole)copper(II)diacetate [19]. Also the assignment of Cu-O vibrations is not easy. By comparison with other similar systems [15,19] two of these vibrations have been assigned tentatively to the bands located at 634 and 359 cm⁻¹.

Solubility and lipophilicity assays

In order to facilitate future pharmacological studies with this complex we have tested its solubility in a series of common solvents. It is practically insoluble in water, ethanol, methanol, chloroform, methylene chloride, acetone, n-butanol, ethyl ether, bencene, dimethylformamide and dioxane.

On the other hand, we have also tested the stability of suspensions in two usual dispersing agents for medicinal products, i.e., propylene glycol and Tween 80 (sorbitan mono-9-octodecenoate poly(oxy-1,2-ethane-diyl) derivatives, often also called Polysorbate 80 [20]. Both systems generate stable suspensions, although that of propylene glycol appears as somewhat more stable and produces a finer dispersion of the complex. The suspension of Tween 80 appears also very interesting for pharmacological studies because, due to its higher viscosity, the complex can probably be liberated more slowly.

Finally, we have also undertaken a standard lipophilicity test, determining the water/n-octanol partition coefficient [10]. A figure of 0.25 ± 0.02 was determined for the partition coefficient. This value is unexpectedly low in comparison with that of free sebacic acid (ca. 20) [10], taking in account that in the case of numerous aminoacids, the respective Cu(II) complexes clearly present higher values than those of the free ligands [11].

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