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Vibrational spectra of clioquinol and its Cu(II) complex

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The infrared and Raman spectra of 5-chloro-7-iodo-8-hydroxyquinoline (clioquinol, CQ) and that of its Cu(II) complex of stoichiometry $[Cu(CQ)_2]$ were recorded and briefly discussed. Some comparisons were made with related complexes. The interest of the investigated systems in relation to Alzheimer's disease is briefly commented. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: clioquinol; copper(II) complex; infrared spectra; Raman spectra; Alzheimer's disease

INTRODUCTION

Alzheimer's disease (AD) is the main form of dementia, characterized by the loss of cholinergic neurons and the progressive deterioration of cognitive function, memory and self-care. It has long been associated with the accumulation of insoluble amyloid 'plaques' in the brain. These plaques are formed by a process called *amyloidosis*, whereby a 40- to 43-residue peptide called β-amyloid (Aβ) aggregates into insoluble fibers.[1,2] Many other neurodegenerative diseases have been associated with the aggregation of specific proteins or peptides in different parts of the brain, including Parkinson's disease, Huntington's disease and prions diseases.[2]

On the other hand, increasing evidence indicates that metal ion homeostasis is altered in AD and a number of metal cations such as Zn(II), Cu(II) and Fe(III), accumulate in the neuropil of the AD brain and are further enriched within amyloid deposits. In particular Aβ binds these metal ions very avidly and this may explain their enrichment in plaque pathology. Plaque deposits also generate oxidative stress, which may originate from the formation of free radicals in the presence of redox-active metal cations.[3]

Copper and zinc also interact with the amyloid precursor protein (APP) and the precipitation of Aβ is also related with the presence of these metal cations.[3–5] Therefore, taking into account the importance of these metals, it has been suggested that their regulation may be effective as a novel protection mechanism against AD. The search for compounds capable of interfering selectively with pathological metal metabolism in the brain suggested that clioquinol (CQ) (5-chloro-7-iodo-8-hydroxyquinoline, Fig. 1) may be particularly useful in this context.[4–7]

CQ is a United States Pharmacopoeia antibiotic, which was formerly used as an anti-infective and antiamebic agent, has now been withdrawn.[8] Its favorable pharmacological effects are probably related to its high lipophilicity, which facilitates its penetration through the blood–brain barrier.[5] Studies with a transgenic mouse model of AD (Tg2576) have shown that CQ markedly reduces Aβ precipitation in the brain and, consequently, could be clinically useful.[3–7] Besides, this treatment did not induce a loss of metal levels systemically, probably because it is a relatively weak chelator, and the metals may be redistributed rather than excreted after CQ administration.[5,6]

A first insight into the structural characteristics of the complex, which Cu(II) forms with CQ, was obtained only very recently through single crystal X-ray diffractometric studies.[9] Thus, it seems interesting to perform a vibrational spectroscopic study of this complex and to compare them with the spectroscopic behavior of free CQ.

EXPERIMENTAL

CQ was purchased from Aldrich and used as supplied. All the other reagents and solvents were Merck analytical grade products.

The Cu(II) complex was obtained in the form of pale orange crystals by slow evaporation in air of a DMF solution of CQ to which the required amount of an aqueous solution

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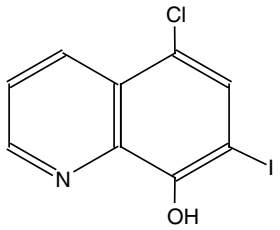

Figure 1. Schematic structure of clioquinol (CQ).

of copper sulfate was added, at a 1 : 2 Cu/CQ molar ratio. The purity of the complex was checked by elemental analysis, confirming the $[Cu(CQ)_2]$ stoichiometry.

The infrared spectra were recorded on a Bruker IF 66 FTIR spectrophotometer in the spectral range between 4000 and 400 cm^{-1}, using the KBr pellet technique. A total of 80 scans was accumulated. Raman spectra were obtained with the FRA 106 accessory of the above-mentioned instrument. The radiation of 1064 nm from a Nd : YAG laser was used for excitation.

RESULTS AND DISCUSSION

Structure of the complex

In the complex, CQ coordinates to the metal center through its deprotonated phenolic group and the pyridine N-atom, resulting in the neutral ML_2 species. $[Cu(CQ)_2]$ presents a planar structure, with the donor atoms of the two ligands arranged in the *trans* position.[9]

Vibrational spectra

Vibrational spectra of free clioquinol

The infrared and Raman spectra of CQ are shown in Figs 2 and 3, respectively. The proposed assignment, presented in Table 1, performed on the basis of some standard references[10,11] and with the help of the results derived from the investigation of related systems,[12–14] is briefly reported as shown in the list.

– The relatively strong and broad IR band centered at 3068 cm^{-1} (not shown in Fig. 2) can be related to the phenolic *O*–H stretching motion and the broadening probably originated in the participation of ν(C–H) ring stretching vibrations. In this region, the Raman spectrum presents only a strong and well-defined band at 3070 cm^{-1}, also related to ring C–H stretching vibrations. The ν(OH) vibration is found in a similar range as in 8-hydroxyquinoline (*oxine*) itself[15] as well as in other 5-7-halogen-substituted oxines.[14] This band is not present in the metallic complexes of CQ, where the deprotonated O-atom is one of the coordinating centers.
– The two expected δ(OH) deformational modes are difficult to identify because they lie in the same region in which a number of important δ(CH) vibrations or ring motions are found.
– The assignment of the C═N and C═C stretching modes is supported by previous investigations,[12,13] and also these vibrations are located in similar ranges as in other dihalogenated oxines.[14]
– Deformational CH modes, ring breathing and ring deformation vibrations are found in the usual ranges. The C–Cl stretching mode is also found in the usual range for this bond in ring systems.[10] The corresponding C–I mode could not be identified with certainty.
– The ν(C–O) stretching motion and the corresponding deformational vibration are found in the same ranges as in other dihalogenated oxines.[14]

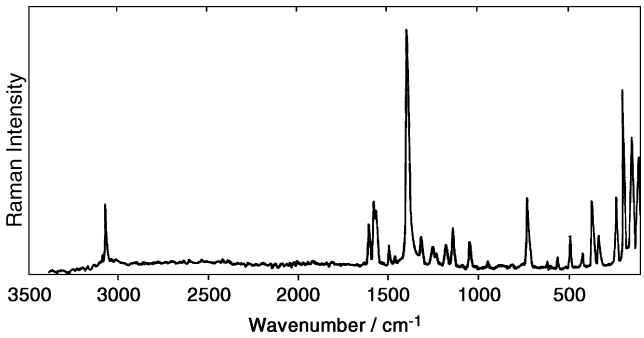

Figure 3. FT-Raman spectrum of clioquinol in the spectral range 3500–100 cm^{-1}.

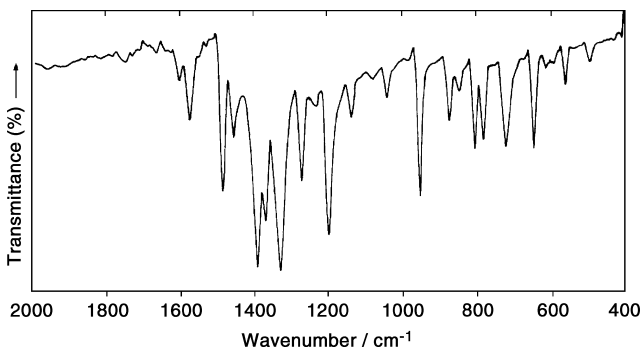

Figure 2. FTIR spectrum of clioquinol in the spectral range 2000–400 cm^{-1}.

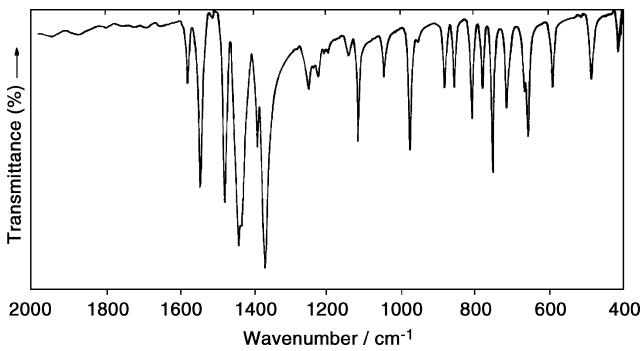

Figure 4. FTIR spectrum of the copper(II) complex of clioquinol in the spectral range 2000–400 cm^{-1}.

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Table 1. Wavenumbers (cm^{-1}) and assignment of the vibrational spectra of clioquinol (CQ) and its copper(II) complex, $Cu(CQ)_2$[a]

Clioquinol		$Cu(CQ)_2$		
IR, ν (cm^{-1})	Raman, ν (cm^{-1})	IR, ν (cm^{-1})	Raman, ν (cm^{-1})	Assignments
3068 s, br	3070 s	–	3064 s	$\nu(O-H) + \nu(CH)$
1604 w	1605 m	1577 w	1579 s	$\nu(C{=}N)$
1576 m, 1530 vw	1573 s,1550 sh	1547 s	1545 m	$\nu(C{=}C)$
1489 vs	1492 w	1481 s	–	$\nu(CC)$
1458 m	1464 vw	1446 vs	–	+
1394 vs,1371 m	1388 vs	1392 w,1375 vs	1369 vs	$\delta(CH)_{in\ plane}$
1331 vs	1315 w	–	–	–
1271 s	–	1248 w	–	$\delta(CH)_{in\ plane}$
1232 w	1246 w,1225 sh	1221 vw	–	+
1200 vs	1777 w	–	–	$\delta(OH)$
1136 m	1136 m	1140 vw	–	–
1082 w	1081 vw	1115 m	1133 s	$\nu(C-O)$
1041 m	1045 m	1045 w	1048 vw	$\nu(C-Cl)$
982 w	950 vw	976 m	964 m	–
953 vs, 874 s	–	881 m	–	–
849 w	–	856 m	–	$\delta(CH)_{out\ of\ plane}$
806 s	808 vw	808 m	–	–
785 s	–	779 w	–	Ring breathing
–	–	754 s	756 s	–
723 s	730 s	–	–	+
715 sh	688 vw	715 m	–	$\delta(OH)$
648 s	667 w, 658 m	–	–	–
615 w	–	–	–	δ_{ring}
593 w, 563 m	565 w	590 m	583 m	–
496 w	495 m	484 m	501 s	$\delta(C-O)$
–	–	–	459 m	$\nu(Cu-O)$
–	428 w	–	–	–
433 vw, 412 vw	–	409 w	–	–
–	374 s, 331 m	–	–	–
–	239 s	–	240 s	–
–	196 vs, 145 vs	–	183 s, 166 s	–
–	110 s	–	112 s	–

[a] s, strong; m, medium; w, weak; sh, shoulder; v, very; br, broad.

Vibrational spectra of the copper(II) complex of clioquinol

The FTIR and Raman spectra of $Cu(CQ)_2$ are shown in Figs 4 and 5, respectively. The proposed assignment is included in Table 1 to facilitate comparisons with the free ligand.

After coordination, the IR peak at 3068 cm^{-1} disappears and only a relatively broad feature centered at 3400 cm^{-1} is observed, confirming that the peak may be related to the ν(OH) stretching vibration. In the Raman spectrum the strong 3070 cm^{-1} band is only slightly displaced to lower energies, confirming its ν(CH) origin.

The $\nu(C{=}N)$ band is displaced to lower wavenumbers in the complex, a fact that can be related with the donor character of the nitrogen atom in the N–Cu bond, which generates a decrease of the electronic density of the ring.[14] Also the $\nu(C{=}C)$ band is slightly displaced to lower wavenumbers in the complex, probably because of the same effect.

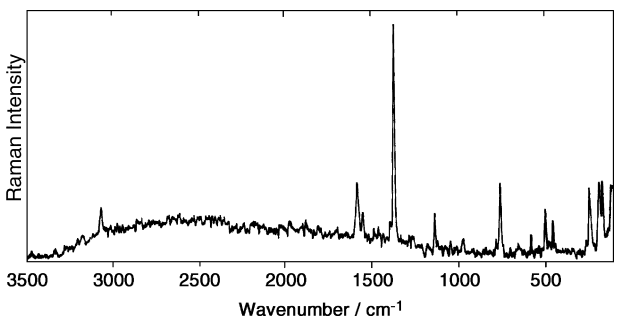

Figure 5. FT-Raman spectrum of the copper(II) complex of clioquinol in the spectral range 3500–100 cm^{-1}.

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As the *O*–H group is transformed to a C–*O*–Cu bond in the complex, some changes in position and band intensities are observed in the spectral range in which δ(CH) and δ(OH) modes are located. This metal-to-ligand interaction also produces a slight increase of the ν(C–O) stretching after complex formation. In the case of the corresponding δ(C–O) vibration this shift is not so evident, although the Raman data also suggests a slight energy increment in the complex.

The Cu–O and Cu–N vibrations in the complex could not be identified with certainty. Tentatively, the medium intensity Raman band observed at 459 cm^{-1} has been assigned to a Cu–O stretching motion. Available data of VO^{2+} complexes of halogenated oxines and related ligands[14,16] suggest that the Cu–N vibrations should be located at lower energies.

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