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XAFS study of bioactive Cu(II) complexes of 7-hydroxycoumarin derivatives in organic solvents

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Abstract
We characterize the structure of two Cu(II) complexes of 7-hydroxycoumarins in organic solvents. The solvents are, dimethyl sulfoxide and dimethylformamide. X-ray absorption spectroscopy together with density functional theory calculations are employed to identify the structural changes induced by the two solvents in comparison to the solid form of complexes. We show that the structure of the Cu(II) complexes is modified depending on the solvent and we propose the geometry of the complexes molecule.

Introduction
Life style and environmental factors cause increase of new mechanisms of bacterial and viruses resistance. As an answer to that an intensive work is being done among others in a field of metal-organic ligand complexes. New biologically active compounds are being looked for and the biggest attention is focused on these which occur in nature like coumarins and their derivatives. The natural as well as synthetic coumarins, therein hydroxycoumarins, have a large spectrum of biological activity. Such derivatives proved theirs usefulness as anti-coagulants [1], antibacterial agents [2], antifungal agents [3], biological inhibitors [4], chemotherapeutics [5] and as bio-analytical reagents [6]. Moreover, discovery that their complexes with metal ions can be more effective than the parent ligands, opened a new field of drug research. Recent studies showed that such complexes can be successfully used in a treatment of bacterial infections or even cancer [7]. The hydroxycoumarins are able to act as potent metal chelators and free radical scavengers. In many cases the metal complexes are more potent and less toxic as compared to the parent drug.
Complexes usually are difficult to crystalize and then X-ray diffraction technique is inapplicable. In such a case structural information for such complexes is rather approximated than experimentally determined. Being a local structural technique, X-ray absorption spectroscopy (XAS) is an ideal tool to structurally describe compounds regardless of their crystal form or state. XAS provides information about the local atomic order, coordination number, kind of atoms, oxidation state, relative disorder and even angles between central atom and near neighbors [8-10]. Data obtained from XAS combined with the DFT calculations allow building structural models of the complexes. This combination proved its usefulness e.g. in case of structural studies of bioactive hydroxycoumarin complexes [7]. In this article we want to show that such approach is also appropriate for complexes in solutions. The goal was to use extended X-ray absorption fine structure (EXAFS), X-ray absorption near edge structure (XANES) simulations and density functional theory (DFT) calculations to structurally describe Cu(II) complexes of 7-hydroxycoumarin derivatives in organic solutions. The complexes were: (*i*) Cu(II) complex with 6-acetyl-7-hydroxy-4-methyl-coumarin **1** and (*ii*) Cu(II) complex with 8-acetyl-7-hydroxy-4-methylcoumarin **2**. Due to the fact that these complexes were insoluble in water, commonly used organic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF)

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were used. The aim is to investigate whether the presence of the solvent molecules modifies the structurally bioactive complexes.

Experimental

The synthesis of the complexes is described elsewhere [7]. XAS measurements at Cu K-edge in fluorescence mode were performed at XAFS beamline at Elettra synchrotron (Trieste, Italy) [11]. Double crystal Si 111 monochromator was calibrated using Cu foil. The solutions were placed in a cell with 3 mm of thickness along the X-ray beam. Both complexes were dissolved in DMSO and DMF, and the solutions with 1mmol/dm^3 concentrations of complexes were exposed to the synchrotron radiation. It should be pointed that samples were measured at room temperature. In order to estimate oxidation state of studies complexes reference Cu_2O and CuO were measured in transmission mode. EXAFS data were analyzed using IFFEFIT package [12-13]. The quantitative analysis of EXAFS spectra of dissolved complexes was performed as follows: k^2 weighted $\chi(k)$ data were Fourier transformed in the k range 2.5–8 for **1** in DMSO, 2.5–10 for **1** in DMF as well as **2** in DMSO and DMF. The Fourier's back transformation ranges were from 1 to 3 Å for complexes **1** in DMSO and **2** in DMF. In case of **1** in DMF and **2** in DMSO ranges were from 1 to 2.5. The amplitude reduction factor ($S0^2$) was estimated based on reference Cu oxides and later evaluated during fitting procedure. Its value was around 0.8. XANES spectra were calculated using full potential multiple scattering theory framework (FPMS) code [14-15]. Broadening of spectra due to polarization of valence shell by photoelectron was taken into account with MXAN software [16-17]. DFT calculations were performed with Turbomole ver. 6.5 computational package [18]. Perdew-Burke-Ernzerhof (PBE) gradient exchange–correlation functional [19] was applied along with def2-TZVP Gaussian basis set [20-21] and Grimme correction of dispersion interactions [22]. The influence of bulk solvent was approximated by COSMO approach [23].

Results

XAS technique allows studying compounds regardless of their crystal form or state. This experimental method was also previously used in studies of microcrystalline powders [8-10]. Here we report the results, obtained by using combination of XAS and DFT, for Cu(II) complexes **1** and **2** dissolved in two polar aprotic solvents: DMSO and DMF.

Figure 1a shows the XANES spectra of complexes in both powder and liquid form. In figure 1b first derivatives of solutions are compared with Cu_2O and CuO. One can notice that position in energy of the absorption edge for studied complexes agrees with CuO. That points out that in all complexes Cu is mostly at 2+ state. Moreover, some pre-edge features characteristic for Cu(II) complexes, can be observed. Their intensity is very week what suggests that all complexes are centrosymmetric. [24, 25].

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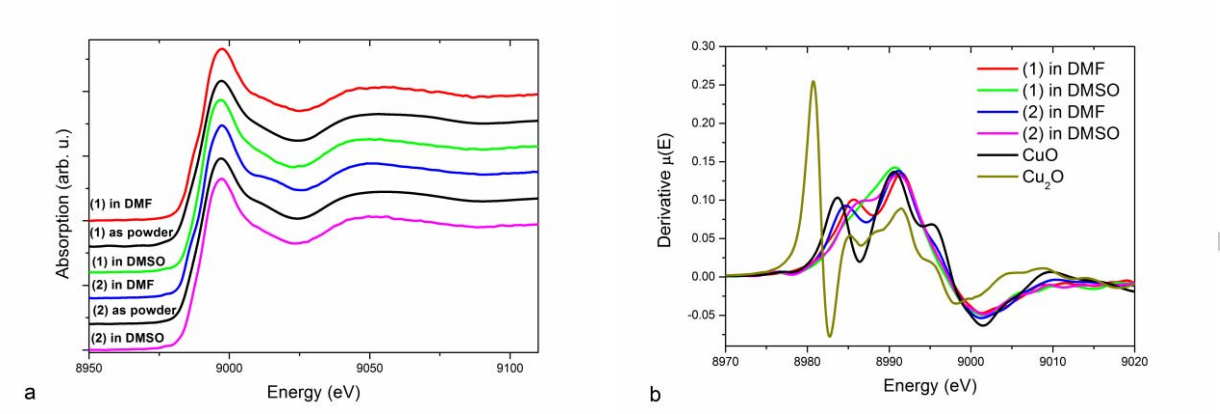


Figure 1 (a) The experimental XANES Cu K–edge spectra of complexes in solid and liquid state. (b) XANES first derivatives of complexes and reference Cu_2O and CuO.

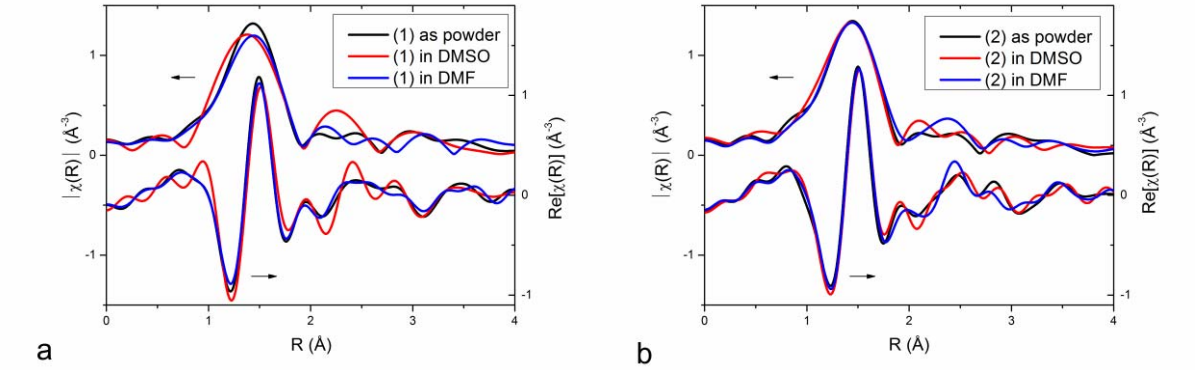


Figure 2. Moduli of the Fourier transform (FT) of the EXAFS oscillations of the complexes, **1** (panel a) and **2** (panel b) in powder and dissolved forms. For better visibility of differences, comparison of real part was also presented for each complex.

Figure 2 shows the comparison between the Fourier transform (FT) of the EXAFS oscillations, as both magnitude and real part, of the two complexes in powder and dissolved forms. In the case of complex **1** the molecular structure of the solid form was modified by the DMSO while the DMF solvent did not cause any significant changes. In the case of complex **2** the situation is the opposite, DMSO did not modify the structure while DMF did. According to previously obtained structural information on microcrystalline complexes, in both cases two ligands are bidently coordinated with Cu(II) cation via the acetyl and deprotonated hydroxyl O atoms (Fig. 2). In both complexes the coordination sphere has flat square geometry and consists of four oxygen atoms. The distance of oxygen atoms to the central Cu cation was found to be 1.93(4) and 1.93(1) Å respectively for (1) and (2) [7]. Despite their similarities in coordination polyhedra the complexes significantly differ in biological activity.

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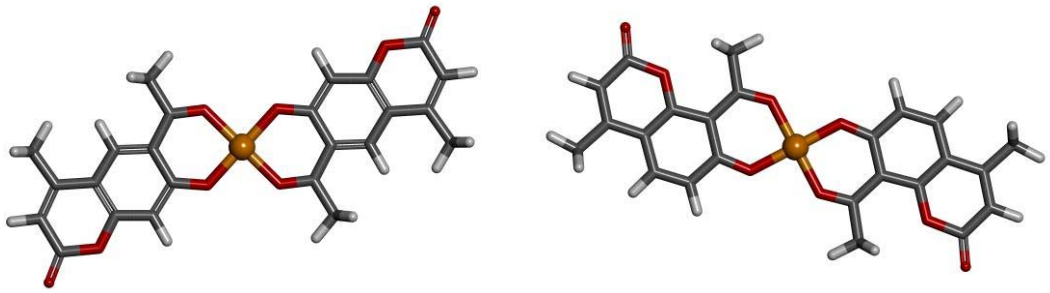


Figure 2. Molecular structures of complexes **1** (left) and **2** (right) in a powder form [7].

Detailed EXAFS analysis indicated that for complex **1** dissolved in DMSO, the first coordination sphere was not changed *i.e.* four oxygen atoms are located at the distance around 1.9 Å. Additionally two sulphur atoms were identified at the distance around 3 Å, indicating that DMSO molecules are attached to the complex (see Table 1). In the case of **1** in DMF solution analysis revealed that no structural change occurred with respect to the solid form.

For complex **2** in DMSO solution no structural changes in comparison to microcrystalline form were observed. For DMF solution the first coordination sphere is preserved with four oxygen atoms at the distance around 1.9 Å. In the next coordination sphere, two oxygen atoms at the distance around 2.5 Å and two carbon atoms at distance around 3.4 Å were identified, which suggests coordination of two DMF molecules via oxygen atoms. Figure 3 shows the comparison between the modulus of the FT of the experimental EXAFS oscillations and the best fit calculation. The numerical output of the fitting results for both complexes and solvents are gathered in Table 1.

Complex	Bond	R [Å]	N	σ^2 [Å^2]	*R*-factor
1 in DMSO	Cu-O	1.92(4)	4	0.003(1)	0.01
	Cu-C	2.86(1)	4	0.004(3)	
	Cu-S	3.04(3)	2	0.016(9)	
	Cu-C	3.27(4)	2	0.004(3)	
1 in DMF	Cu-O	1.93(2)	4	0.004(2)	0.01
2 in DMSO	Cu-O	1.94(1)	4	0.004(1)	0.01
2 in DMF	Cu-O	1.93(4)	4	0.004(2)	0.01
	Cu-O	2.49(6)	2	0.004(2)	
	Cu-C	2.85(3)	4	0.005(2)	
	Cu-C	3.37(8)	2	0.005(2)	

Table 1. EXAFS parameters of Cu(II) complexes: distance—R, number of atoms in a coordination sphere—N, Debye–Waller factor—σ^2 and R-factor.

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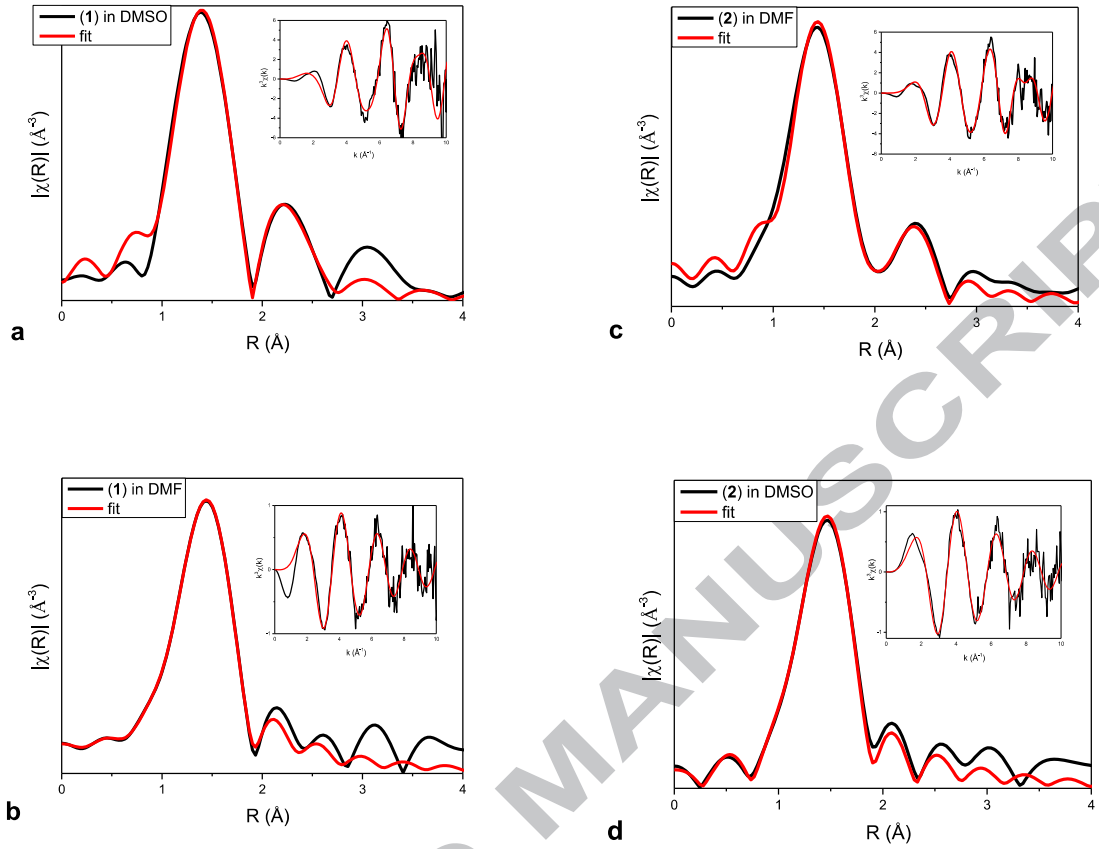


Figure 3. Moduli of the Fourier transformed experimental EXAFS oscillations for complexes **1** (panel a and b) and **2** (panel c and d) (black line) and best fit (red line). The insets show EXAFS oscillations together with the best fit.

The information obtained from EXAFS analysis was used as a starting point for DFT calculations. DFT optimized models of **1** in DMSO and **2** in DMF adducts are shown in Figure 4. Selected geometrical parameters are summarized in Table 2. The bond lengths predicted by DFT in the Cu(II) coordination sphere are in very good agreement with EXAFS data. Models from EXAFS optimized by DFT were used in XANES spectra calculations, where FPMS code was applied. The calculated and experimental XANES spectra are in good agreement (see Figure 5 a and b) which confirms the validity of proposed models.

Summarizing, complexes **1** in DMF and **2** in DMSO preserve unchanged square planar coordination with four oxygen atoms at the corners, as found in solid samples [7].
Around the Cu(II) cation in complex **1** in DMSO and complex **2** in DMF the tetragonal bipyramid has been formed. In both cases two solvent molecules are present as axial ligands. In the case of **1** in DMSO solvent molecules are bonded via sulphur atoms. For **2** in DMF solvent molecules are bonded via oxygen atoms.

	1 in DMSO	**2** in DMF
$Cu\text{-}O_{acetyl}$	1.997	1.968

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Cu-O_{phenol}	1.925	1.933
Cu-X[1]	3.006	2.595
Cu-C_{acetyl}	2.929	2.895
Cu-C6/C8	2.901	2.840
Cu-C7	3.323	3.231

[1] Solvent atom bound to Cu: S in **1**, O in **2**.

Table 2. Selected calculated bond distances (Å) of complexes **1** in DMSO and **2** in DMF.



Figure 4. DFT optimized molecular structures of complexes **1** in DMSO (left) and **2** in DMF (right)**.**

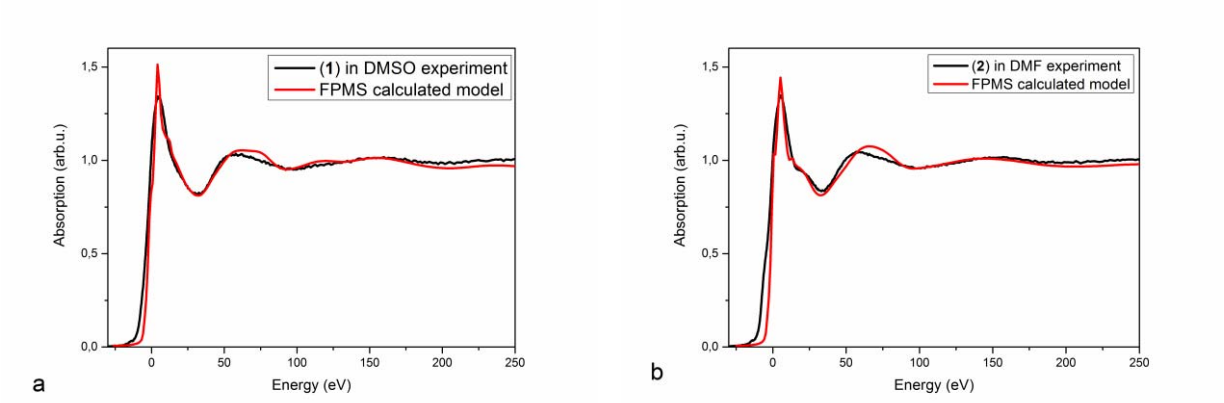


Figure 5 FPMS calculated XANES spectra compared with experimental: a) complex **1** in DMSO and b) complex **2** in DMF.

Conclusions

We have characterized the molecular structure of Cu(II) complexes of 7-hydroxycoumarins in organic solvents: DMSO and DMF by combining XAS and DFT. We have shown that the first coordination sphere of the solid complexes does not change in solution and in both cases, the hydroxycoumarin ligands are coordinated in the bidentate mode to the Cu(II) cation through the acetyl and deprotonated hydroxyl O atoms. Regarding higher coordination shells, coordinating DMSO molecules are found in complex **1**, and DMF molecules in complex **2**. For them, the centrosymmetric

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coordination polyhedron of Cu(II) exhibits tetragonal bipyramidal geometry with four oxygen atoms from coumarin ligands in plane, and two sulphur (for **1** in DMSO) and oxygen (for **2** in DMF) atoms, in axial positions from solvents.

We have showed that the combination of theoretical calculations and experimental methods of exploring local structure is able to describe molecular structure of bioactive 7-hydroxycoumarin complexes with copper(II) in organic solvents. Moreover, structural differences have been found and described.

ACKNOWLEDGEMENTS

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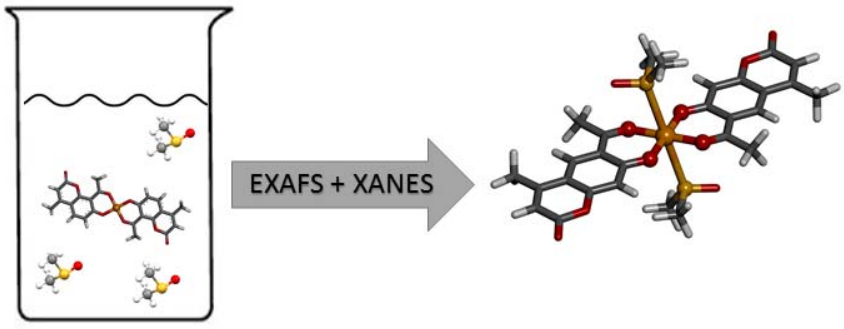
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Graphical abstract



Highlights

- Geometry of two Cu(II) complexes of 7-hydroxycoumarins in organic solvents have been determined,
- Molecular structure of the complexes have been studied by XAS and DFT,
- Coordination of DMSO through sulphur atom have been found for Cu(II) complex with 6-acetyl-7-hydroxy-4-methyl-coumarin,
- Coordination of DMF through oxygen atom have been found for Cu(II) complex with 8-acetyl-7-hydroxy-4-methyl-coumarin.

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