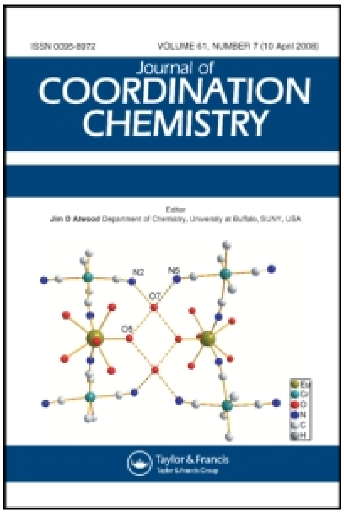

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A NEW BIOINORGANIC COMPLEX: EXAFS ANALYSIS AND MOLECULAR MODELLING OF A *BIS*-$CuBr_2$ COMPLEX OF $6^A,6^B,6^D,6^E$-TETRA-*o*-NICOTINOYL-α-CYCLODEXTRIN

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Chemically modified $6^A,6^B,6^D,6^E$-tetra-*o*-nicotinoyl-α-cyclodextrin forms a 1 : 2 complex with $CuBr_2$. EXAFS analysis has been performed on this complex showing direct Cu-macrocycle coordination *via* the nicotinate groups. Two nitrogen and two bromide atoms are at an average distance of 1.99 and 2.46 Å from the copper, respectively. A structural model has been built using molecular dynamics simulation, consistent with the EXAFS results.

Keywords: $[6^A,6^B,6^D,6^E$-tetra-*o*-nicotinoyl-α-cyclodextrin$]\cdot 2CuBr_2$; bioinorganic complex; EXAFS; molecular modelling

INTRODUCTION

Cyclodextrins, cyclic oligosaccharides consisting of 6, 7 or 8 α-(1-4)-linked glucose units, have been used as catalysts, enzyme mimics, drug carriers and food stabilizers. Their use is restricted by the fact that the only chemical group attached to the ring is the hydroxyl group. The specifically modified cyclodextrins – hydroxyl groups substituted by other chemical groups – have opened a way to other applications. In particular, to increase metal–cyclodextrin complexation four (6^A, 6^B, 6^D and 6^E) of the six primary

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hydroxyls of a α-cyclodextrin were selectively substituted by nicotinate groups. The obtained molecule $6^A,6^B,6^D,6^E$-tetra-*o*-nicotinoyl-α-cyclodextrin forms complexes with $CoCl_2$, $CuBr_2$ and $PtCl_2$[1,2] in a 1 : 2 ratio. Electronic spectra of the Co complex and an ^1H NMR study of the Pt compound accompanied by molecular graphics have permitted a description of the metal coordination in these compounds, but all attempts to characterize the copper system with the above techniques were not satisfactory.[3]

The suitability of EXAFS[4] (extended X-ray absorption fine structure) for the study of local coordination of metal compounds is well established. In this work, the copper coordination in the solid compound $[6^A,6^B,6^D,6^E$-tetra-*o*-nicotinoyl-α-cyclodextrin$]\cdot 2CuBr_2$ is analyzed by this technique. Using these results structural models of the complex were computed by molecular dynamics simulations. The present investigation was undertaken during the course of research on new bioinorganic ligands.

EXPERIMENTAL

Preparation of Compounds

$[6^A,6^B,6^D,6^E$-tetra-*o*-nicotinoyl-α-cyclodextrin$]\cdot 2CuBr_2$, stable in air and room temperature, precipitates immediately upon addition of $CuBr_2$ to a solution of the macrocycle in acetone. After filtering, washing with methanol and drying *in vacuo*, the solid was powdered to prepare the EXAFS samples.

Crystalline $Cu(C_5H_5N)_2Br_2$,[5,6] used as the EXAFS standard compound, was obtained spontaneously from the inclusion compound $Cu(C_5H_5N)_4Br_2\cdot(C_5H_5N)_2$[7] by its standing in air at room temperature during six hours; it is the pyridine desorption product.

EXAFS Analysis

Absorption data were collected at the copper K_α absorption edge on the EXAFS-I station of LURE-DCI (the French synchrotron radiation facility). Ring energy: 1.85 GeV; current range: 200–300 mA; monochromator: channel-cut Si(311); step by step transmission mode; energy resolution: 2 eV; energy range: 8850–9600 eV; room temperature; detectors: two ion chambers filled with an air–argon gas mixture.

The EXAFS spectra were obtained following a standard procedure,[8] from the experimental absorption data after subtraction of the absorption background. This background was obtained by fitting the region below the absorption edge with a Victoreen expression which was extrapolated beyond the edge. The background absorption coefficient μ_0 was simulated by using a three region cubic spline through the EXAFS oscillations after the edge. The remaining long wavelength oscillations were removed with a smoothing procedure. In converting the scale from photon energy E to the wave vector k of the ejected electron $k = \sqrt{(2m_e/h^2)(E - E_0)}$, E_0 was fixed at the inflexion point of the copper edge.

The k^3 multiplied spectra of compounds were Fourier transformed (FT) in the 2.7–11.7 Å^{-1} range. The peaks were filtered and inverse-transformed. The resulting spectrum of [6^A,6^B,6^D,6^E-tetra-*o*-nicotinoyl-α-cyclodextrin]·$2CuBr_2$ was fitted with theoretical amplitude and phase parameters,[9] which were tested on the standard compound $Cu(C_5H_5N)_2Br_2$. In this method, experimental errors for the fitted parameters are within ±12% and ±0.02, for atom number and bond distance, respectively.

Programs: EXAFS analysis package,[10] running on a personal Pentium60 computer.

EXAFS RESULTS

In the crystal structure of $Cu(C_5H_5N)_2Br_2$ the copper presents a *pseudo*-octahedral coordination; the metal is bounded to four shared bromide atoms and two pyridines, with two bromides located at a shorter distance (2.451(1) Å) than the others (3.240(1) Å). Figure 1(a) displays the EXAFS oscillations and Figure 1(b) its FT (*pseudo*-radial atomic distribution). The first and second peaks correspond to contributions of pairs $Cu-N_2$ and $Cu-Br_2$, the other peaks – not resolved – are contributions of pairs formed with neighbor atoms placed farther than 3 Å. The theoretical amplitudes and phases necessary to fit the FT filtered peaks were adjusted on this compound. The fitted parameters of the standard compound are presented in Table I. The distances and the number of atoms obtained fit the X-ray diffraction results.

Absorption spectra of [6^A,6^B,6^D,6^E-tetra-*o*-nicotinoyl-α-cyclodextrin]·$2CuBr_2$ and the Fourier transform of the EXAFS oscillations are shown in Figure 2(a) and (b). The best fit of the filtered peaks, using the theoretical amplitudes and phases adjusted on the standard compound, gives two nitrogen and two bromide atoms at 1.99 and 2.46 Å from the copper, respectively (Table I). Figure 2(c) illustrates the experimental and calculated FT.

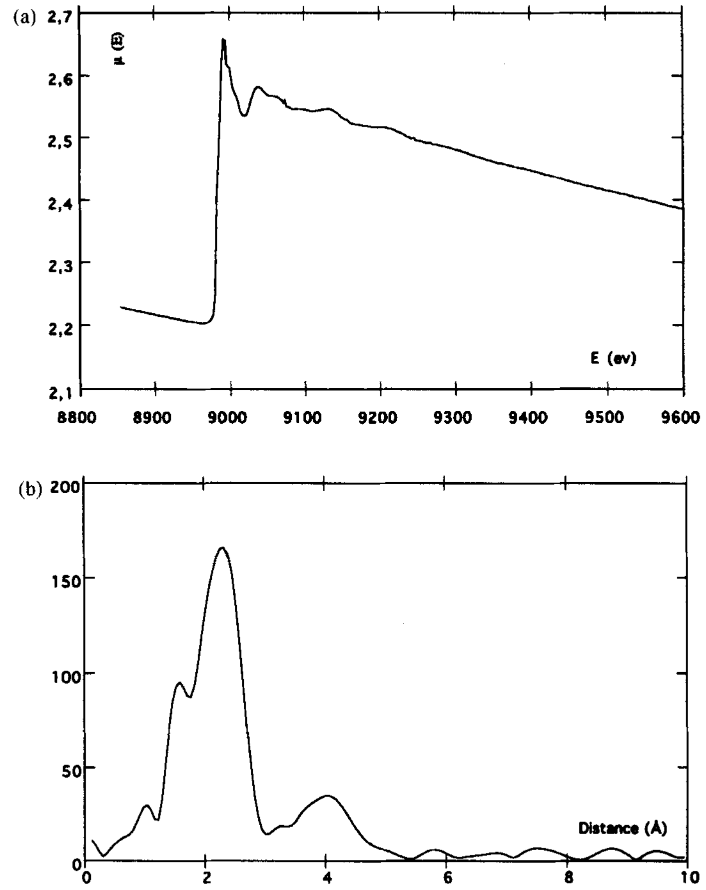

FIGURE 1 $Cu(C_5H_5N)_2Br_2$; (a) absorption spectrum on CuK_α edge; (b) Fourier transform of the EXAFS oscillations.

TABLE 1 Fitted parameters with theoretical amplitudes and phases, for the standard compound $Cu(C_5H_5N)_2Br_2$ and for [$6^A,6^B,6^D,6^E$-tetra-*o*-nicotinoyl-α-cyclodextrin] · $2CuBr_2$

Compound	*Pairs*	N_i	R_i (Å)	$R_{X\text{-ray}}$ (Å)	σ_i (Å)	E_0 (eV)
$Cu(C_5H_5N)_2Br_2$	Cu–N	2	2.01(2)	2.013(5)	0.09	−9.8
	Cu–Br	2	2.48(4)	2.451(1)	0.09	−13.3
[$6^A,6^B,6^D,6^E$-tetra-*o*-nicotinoyl-α-cyclodextrin] · $2CuBr_2$	Cu–N	2	1.99(2)	—	0.09	−9.8
	Cu–Br	2	2.46(4)	—	0.09	−13.3

The fitted parameters are: the atom number N_i of the *i*th shell, the average distance R_i which separates the absorbing atom from these N_i scattering atoms, the deviation σ_i from this distance R_i and the energy E_0 above which the photoelectron is free.

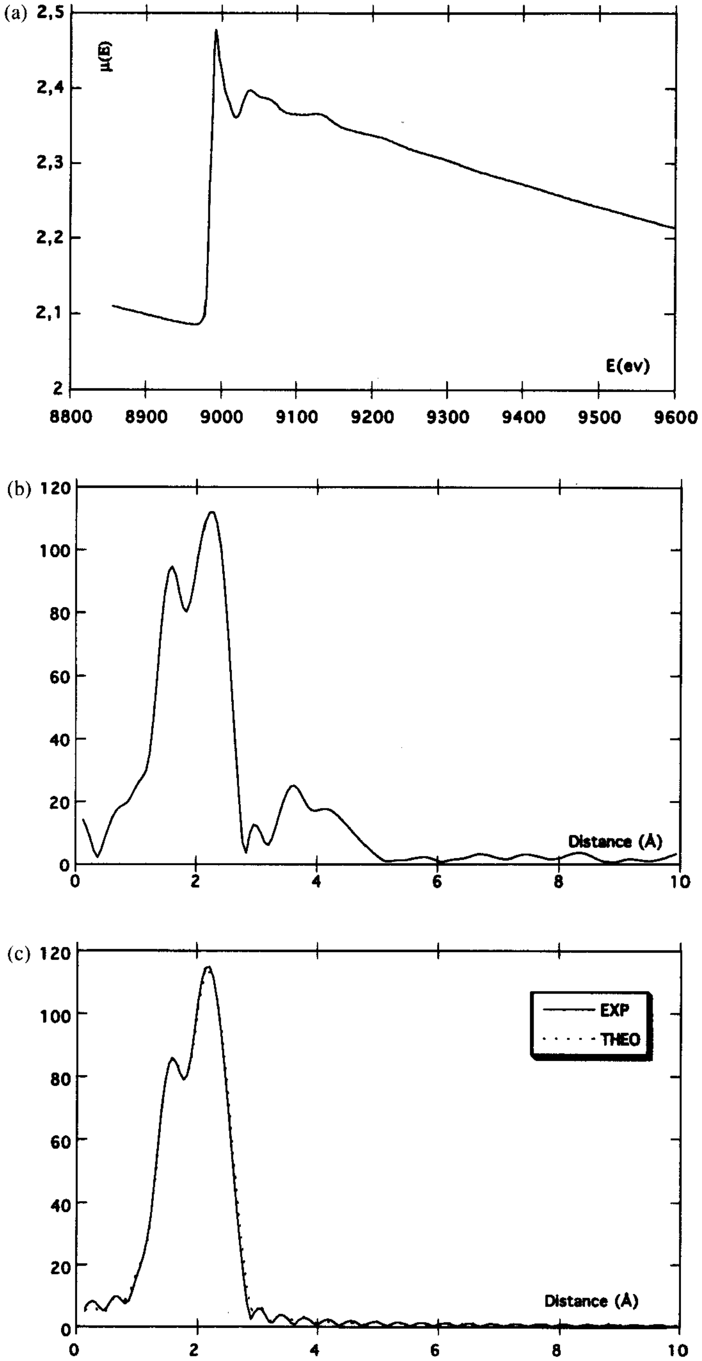

FIGURE 2 $[6^{A},6^{B},6^{D},6^{E}$-tetra-*o*-nicotinoyl-α-cyclodextrin$]\cdot 2CuBr_2$; (a) absorption spectrum on CuK_{α} edge; (b) Fourier transform of the EXAFS oscillations; (c) experimental (—) and calculated (···) filtered Fourier transform.

MOLECULAR MODELLING

Structural models of [6^A,6^B,6^D,6^E-tetra-*o*-nicotinoyl-α-cyclodextrin] · 2Cu-Br_2 have been constructed using a two step conformational analysis; potential energy minimization is followed by simulated annealing iterations. The rationale of this procedure is that the minimization of the potential function in the first step usually leads to the local minimum closest to the starting conformation. The simulated annealing allows to sample a larger part of conformational space.

Potential Energy Minimization

Coordinates of a α-cyclodextrin molecule from the α-CD acetone crystal structure[11] were used and the ion chelation substituents were connected on it and directed outwards the cavity. The molecule presents two bidentate coordination sites,[1] hence two $CuBr_2$ groups were placed with Cu–N and Cu–Br distances as obtained from the EXAFS experiment (Table I).

The potential energy of the molecule was computed taking into account bond stretching, angle bending, out of plane bending, torsional (dihedral) deformation, van der Waals (Lennard–Jones) and electrostatic (Coulomb potential) interactions, using the following expression

$$E_{\text{pot}} = \sum_{\text{bonds}} \frac{1}{2} k^{d_i}(d_i - d_i^0)^2 + \sum_{\text{angles}} \frac{1}{2} k^{\theta_i}(\theta_i - \theta_i^0)^2 + \sum_{\text{out of plane}} \frac{1}{2} K^{d_i} d_i^2$$
$$+ \sum_{\text{dihedrals}} \frac{1}{2} V^{\omega_i}[1 + S_i \cos(|n_i|\omega_i)] + \sum_{i<j} E_{ij}\left(\frac{1}{a_{ij}^{12}} - \frac{2}{a_{ij}^{6}}\right) + \sum_{i<j} \frac{q_i q_j}{\varepsilon r_{ij}}.$$

The potential function of the resulting model was then minimized by a conjugate gradient iterative algorithm. Although solvent molecules usually are included in the cavity, all calculations were performed *in vacuo*, given the preparation of the compound.

Molecular Dynamics Simulated Annealing

In order to collect different minimum energy conformations, a step of molecular dynamics simulated annealing calculation was then performed.

The model obtained by the potential energy minimization was submitted to 100 cycles of simulated annealing by heating during 2000 ps at 2000 K and slowly cooling to 200 K in 1000 ps. In order to account for the flexibility of the molecule at high temperatures, the cyclodextrin macrocycle was allowed to vibrate, but torsion angle constraints were imposed around the anomeric oxygens to avoid cavity distortion at low temperature. The potential energy of each of the 100 resulting conformations was subsequently minimized and the resulting copper cations coordinations analyzed. In eight conformers each one of the two coppers are coordinated to two nitrogen atoms of the pyridyl ligands and two bromide anions, in agreement with the EXAFS experiment. For this coordination, the different structural possibilities superimposed in Figure 3(a) clearly demonstrate the flexibility of the molecule. In all cases the copper cations are tetrahedrically coordinated as illustrated by the example of Figure 3(b).

For the molecular modelling, Version 6.3 of the SYBYL molecular modelling package was used.[12] The program was run on a Silicon Graphics Indigo2 computer.

CONCLUDING REMARKS

EXAFS is the only technique that provides structural information on the local average structure around an X-ray absorbing atom, and which can be applied to amorphous as well as crystalline compounds or solutions.

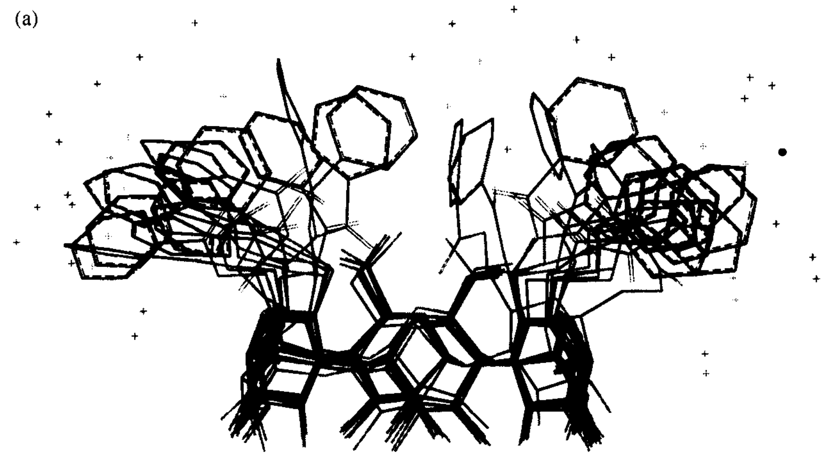

FIGURE 3(a)

(b)

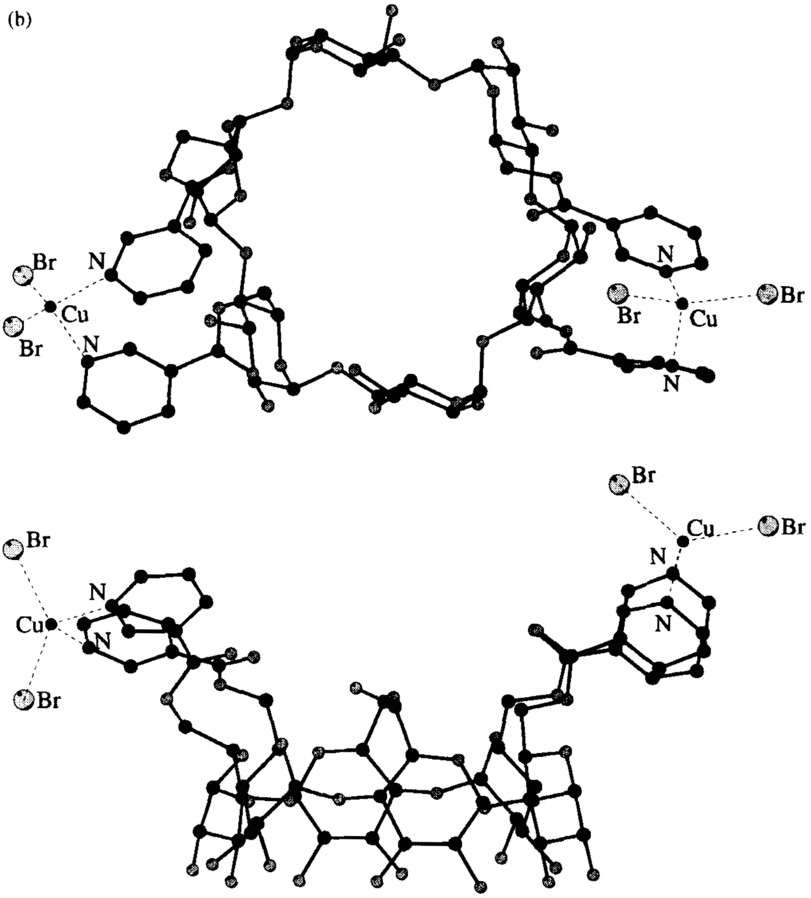

FIGURE 3(b)

FIGURE 3 Structural models of $[6^A,6^B,6^D,6^E$-tetra-*o*-nicotinoyl-α-cyclodextrin$]\cdot 2CuBr_2$; (a) superimposition of the conformers with respect to the EXAFS coordination; (b) tetrahedrical copper coordination (orthogonal projections).

Application of this technique to the $[6^A,6^B,6^D,6^E$-tetra-*o*-nicotinoyl-α-cyclodextrin$]\cdot 2CuBr_2$ system confirms that chemically modified cyclodextrin is a first sphere coordination ligand of copper *via* the pyridyl nitrogen atoms of the nicotinate groups. The copper coordination is completed by two Br^- anions.

Molecular modelling predicts an ensemble of sterically possible structural models; nevertheless, the use of experimental information allows us to discriminate between them. In this work only 8% of the models were compatible with EXAFS data.

Acknowledgements

We would like to thank C.-C. Ling for the preparation of [6^A,6^B,6^D,6^E-tetra-*o*-nicotinoyl-α-cyclodextrin] · $2CuBr_2$.

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