Potential antitumor gold drugs: DFT and XANES studies of local atomic and electronic structure

M A Soldatov1, I Ascone2, A Congiu-Castellano3, L Messori4, M A Cinellu5, A Balerna6, A V Soldatov1, and G E Yalovega1

1 Southern Federal University, Sorge str. 5, 344090 Rostov-on-Don, Russia
2 Synchrotron SOLEIL, 91192 Saint-Aubin, France
3 University of Rome “La Sapienza”, 00185 Rome, Italy
4 University of Florence, 50121 Florence, Italy
5 University of Sassari, 07100 Sassari, Italy
6 LNF, 00044 Frascati, Italy

E-mail: msoldatov@inbox.ru

Abstract. Geometry structure optimization of the potential antitumor agent Au(bipy)(OH)2 was carried out by means of density functional theory simulations. The experimental Au L3-edge X-ray absorption near edge structure (XANES) spectrum of Au(bipy)(OH)2 was obtained. The theoretical Au L3-XANES spectra of the gold(III) complex Au(bipy)(OH)2 were simulated using both the self-consistent real-space full multiple scattering theory within the muffin-tin approximation for the potential shape and the full-potential finite difference method. The comparison of the theoretical spectra with the experimental XANES is discussed. The exact local atomic structure of gold complex Au(bipy)(OH)2 has been defined by two independent ab initio methods.

1. Introduction

In recent years new interest has been focused on gold(III) compounds as potential cytotoxic and antitumor drugs [1]. Indeed, some simple mononuclear gold(III) complexes that are sufficiently stable within a physiological-like environment and display relevant cell killing properties toward selected human tumor cell lines were prepared and characterised. Based on experimental evidence collected so far it is hypothesized that these compounds, at variance with classical platinum(II) complexes, produce their cytotoxic effects through DNA-independent mechanisms [2].

However, the precise biochemical mode of action of cytotoxic gold(III) compounds is still unclear. The nature of the reactions of gold(III) compounds with their biomolecular targets strongly depends on the exact local atomic and electronic structure of the gold(III) center. The X-ray Absorption Spectroscopy methods are very sensitive to the local structure around the absorbing atom. In particular, X-ray Absorption near Edge Structure (XANES) analysis may be successfully used to determine an accurate geometry structure for some molecules [3]. XANES spectroscopy can provide full information about local geometry including not only bond lengths but also the bond angles [4-5]. In the present report we studied local structure of Au(bipy)(OH)2 by means of an advanced XANES analysis and density functional theory simulations which are considered to be powerful tools for the precise determination of the local atomic and electronic structure of molecules and nanoobjects.
2. Experiment and methods of calculation

The gold(III) complex \([\text{Au} (\text{bipy})(\text{OH})_2][\text{PF}_6]\) was prepared according to reported procedures [6]. To a solution of 2,2'-bipyridine in acetonitrile an aqueous solution of \(\text{NaAuCl}_4\) and solid \(\text{KPF}_6\) were added. The resulting yellow suspension was refluxed for 15 h, cooled at room temperature, and filtered off. Recrystallization from acetone-diethyl ether afforded \([\text{Au} (\text{bipy})\text{Cl}_2][\text{PF}_6]\). An aqueous suspension of \(\text{Ag}_2\text{O}\) was added to a solution of \([\text{Au} (\text{bipy})\text{Cl}_2][\text{PF}_6]\) in acetone. The mixture was stirred for 24 h at room temperature. \(\text{AgCl}\) was removed by filtration and the solution evaporated to dryness under reduced pressure. The residue was extracted with acetonitrile and filtered. The pale-yellow filtrate was concentrated to a small volume and diethyl ether was added to give a white precipitate of \([\text{Au} (\text{bipy})(\text{OH})_2][\text{PF}_6]\).

Experimental XANES spectra above the Au L₃-edge were obtained at GILDA beam line at the ESRF synchrotron facility. Geometry structure study was based on theoretical analysis of XANES spectra, which were simulated using full multiple scattering method [7] and finite difference method beyond muffin-tin approximation, implemented in a fdmnes2008 package [8]. Hedin-Lundquist exchange-correlation potential was used for estimating of electronic interactions. A density functional theory (DFT) approach was used as a complementary tool to XAFS analysis for geometry optimization and electronic structure determination of \(\text{Au} (\text{bipy})(\text{OH})_2\). DFT calculations (ADF2008 code) [9] provided precise information on 3D electronic density distribution, bonding energy and HOMO-LUMO orbitals shape. We used TZP basis set and OPBE exchange-correlation potential during our simulations.

3. Results and discussion

Total charge on the \(\text{Au} (\text{bipy})(\text{OH})_2\) molecule has positive value. Therefore geometry structure optimization of \(\text{Au} (\text{bipy})(\text{OH})_2\) was carried out with several parameters (total spin value). The initial structure was based on the structure of a similar gold complex [4]. We implemented a relativistic approach for both simulations, but for model 1 we used zero total spin and total spin 1 for model 2. Results of geometry optimization are presented on table 1. The local environment of the gold atom in \(\text{Au} (\text{bipy})(\text{OH})_2\) consists of two oxygen and two nitrogen atoms. Due to model 1 these neighboring atoms are lying in one plane, but this is not true for model 2. DFT calculations show that the model 1 with the maximal bonding energy is preferable to the model 2.

![Figure 1. Structure of Au(bipy)(OH)₂.](image-url)
Table 1. Selected bond distances (Å) and angles (°) and bonding energy for different model structures (eV).

|                  | Initial model | Model 1 (Total spin 0) | Model 2 (Total spin 1) |
|------------------|---------------|------------------------|------------------------|
| Au-O(1)          | 1.960         | 1.935                  | 2.011                  |
| Au-O(2)          | 1.971         | 1.939                  | 2.013                  |
| Au-N(1)          | 2.040         | 2.026                  | 2.225                  |
| Au-N(2)          | 2.031         | 2.028                  | 2.223                  |
| O(1)-Au-N(1)     | 92.9          | 95.1                   | 90.7                   |
| O(2)-Au-N(2)     | 94.1          | 95.4                   | 90.5                   |
| N(1)-Au-N(2)     | 80.6          | 80.1                   | 73.9                   |
| O(1)-Au-O(2)     | 92.5          | 89.4                   | 111.3                  |
| Bonding energy   | 148.6935      | 151.4399               | 149.2722               |

Theoretical XANES spectra were calculated by means of two methods: full multiple scattering within muffin-tin approximation (FMS) and finite difference method in full potential (FDM)(fig. 2). The FMS method, implemented in feff 8.4 code is very fast and shows good results for bulk structures, but muffin-tin approach makes it unsuitable for small molecules. In case of Au(bipy)(OH)2 FDM full potential simulations are better than FMS simulations in muffin-tin approach. During the XANES analysis we have found the best agreement with experimental data for model 1 (fig. 3): one can see peaks a and b on both experimental and theoretical spectrum for model 1, but they are not readable on the theoretical spectrum for model 2. Energy position of peaks c and d on spectra clearly shows that model 1 is to be preferred. It conforms with the results of density functional theory simulations.

![Figure 2](image-url)

**Figure 2.** Comparison of the experimental Au L₃-XANES of Au(bipy)(OH)₂ with theoretical spectra for model 1 structure calculated using the FMS method (FEFF8.4 code) and FDM theory (FDMNES2008 code).

![Figure 3](image-url)

**Figure 3.** Comparison of the experimental Au L₃-XANES of Au(bipy)(OH)₂ with theoretical spectra for two model structures. XANES spectra were calculated using the finite difference method. All spectra are aligned relative to the energy position of main maximum.

Electronic levels for model 1 were calculated with the previously mentioned parameters. Theoretical HOMO-LUMO GAP is 2.34(5) eV. The shapes of HOMO-LUMO orbitals of Au(bipy)(OH)₂ for model 1 structure were calculated (fig.4-5).
4. Conclusions

We have investigated the local atomic and electronic structure of the gold(III) complex Au(bipy)(OH)$_2$. DFT simulations in relativistic approach shows the most probable structure for Au(bipy)(OH)$_2$ (model 1 from table 1). It is in a good agreement with XANES data analysis. During XANES simulation the spectrum for model 1 has the best agreement with the experimental spectrum. The exact local atomic structure of the gold(III) complex Au(bipy)(OH)$_2$ has been defined by two independent ab initio methods.

References

[1] Sadler P J and Sue R E 1994 Metal Based Drugs 1 107-144
[2] Marcon G, Carotti S, Coronnello M, Messori L, Mini E, Orioli P, Mazzei T, Cinellu M A and Minghetti G 2002 J. Med. Chem. 45 1672-1677
[3] Smolentsev G, Soldatov A V and Feiters M C 2007 Phys. Rev. B 75 144106
[4] Bianconi A 1988 XANES spectroscopy X-ray absorption: principles, applications and techniques of EXAFS, SEXAFS and XANES ed R Prins and D C Koningsberger (New York: Wiley) pp 573
[5] Smolentsev G and Soldatov A V 2006 J. Synchrotron Rad. 13 19
[6] Cinellu M A, Minghetti G, Pinna M V, Stoccero S, Zuccaa A and Manasserob 2000 J. Chem. Soc., Dalton Trans. 1261-1265
[7] Rehr J J, Albers R C 2000 Rev. Mod. Phys. 72 621
[8] Joly Y 2001 Physical Review B. 63 125120
[9] G. te Velde et al 2001 J. Comput. Chem. 22 931-967