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Electrochemical, Spectroscopic and Computational Studies on Complexation of Oxacillin with Cu(II) and Co(II) ions. Synthesis and Ligand Hydrolysis

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In this study, the synthesis and characterization of the complexes of oxacillin with Cu(II) and Co(II) ions are presented. These complexes were characterized by FT-IR spectroscopy and elemental analysis. The complexation process of Cu(II) and Co(II) ions with oxacillin in aqueous medium (Britton-Robinson buffer pH 7.4) was followed by means of square-wave voltammetry. Spectroscopic and elemental analysis results showed that Co(II) and Cu(II) complexes were formed with hydrolysed oxacillin anions. In addition, their stability constants and stoichiometric ratios were determined from voltammetric data. Computational results are in agreement with the experimental findings.

Keywords: Hydrolysis, oxacillin - metal ion complexes, square-wave voltammetry, infrared spectroscopy, density functional theory.

1. INTRODUCTION

Oxacillin (5-methyl-3-phenyl-4-isoxazolyl penicillin sodium, abbreviated as NaOXA), is a *β*-lactam antibiotic and is widely used in the treatment of infections caused from bacteria [1]. Some metal ions play an important role in the transport of *β*-lactam antibiotics in blood plasma [2]. It is well known that transition metal complexes have therapeutic effects [3, 4]. In the complexes of Cu(II) with some bioactive antibiotics, this metal ion behaves as a cofactor of the antibacterial activity [5]. In addition, cobalt is a transition metal that has a physiological importance in many biological processes and also shows some biochemical actions [4, 6]. Cu(II) and Co(II) ions have been widely used to inhibit the growth of harmful microorganisms [7]. Their complexes with some drugs have been the subject of

many research studies [8-15], because of the fact that they have both potential synergetic and biological (antitumor, antibacterial and antifungal) activities [16-19].

The compounds with the *β*-lactam moiety are degradable both in aqueous solutions and in the solid-state with the hydrolysis of the *β*-lactam ring. Moreover, the metal ion binding can play an important role on the physiochemical properties, pharmaceutical activities and also stability of *β*-lactam antibiotics. It was reported that the decomposition of *β*-lactam antibiotics by means of some metal ions (Cu(II), Zn(II), Ni(II), Cd(II), Hg(II) and Co(II)) resulted at the hydrolytic cleavage of the *β*-lactam ring. These metal ions behave a catalyst on the hydrolysis of *β*-lactam antibiotics [20-24]. There are some papers that describe the degradation of oxacillin and its copper catalysed hydrolysis [25-30]. However, no direct evidence that includes the combination of theoretical and experimental data has been reported to support the hydrolytic degradation of oxacillin in the presence of the metal ions.

In the literature, square-wave voltammetry (SWV) has been used to determine the stability constants and stoichiometries of complexes [31, 32]. On the other hand, the density-functional theory (DFT/B3LYP method) with a 6-31G(d,p) basis set and FT-IR spectroscopy methods were applied to investigate the solid state stability of meropenem which is a *β*-lactam antibiotic [33]. The purpose of this study was to examine the interactions of OXA^- with Cu(II) and Co(II) ions in aqueous solution by using SWV technique and also to determine the chemical structures of these complexes from their electrochemical, spectroscopic, elemental analysis and computational data. To our best knowledge, this study is the first for both theoretical and experimental identification of the hydrolytic degradation of OXA^- in the presence of Cu(II) and Co(II) ions.

2. EXPERIMENTAL

2.1. Apparatus

Voltammetric measurements were performed using an EG&G PAR 384B Polarographic Analyser which is connected to an EG&G PARC 303A stand. The three-electrode system consisted of an $Ag|AgCl|KCl_{sat.}$ reference electrode, a platinum wire as a counter electrode and hanging mercury drop electrode (HMDE) as the working electrode. The voltammograms were monitored by ECDSOFT [34] software. pH measurements were made with a Jenway 3010 pH-meter.

Elemental (C, H, N) analyses were carried out by standard methods at GRUMLAB Giresun University Research Centre (Giresun, Turkey). The FT-IR spectra in the 4000-400 cm^{-1} frequency range were recorded from KBr pellets with a Perkin-Elmer System 2000 interferometer.

2.2. Reagents

NaOXA was obtained from Fluka. All other chemicals were of analytical grade and were obtained from Merck. A stock solution of 2.0×10^{-3} M NaOXA was prepared daily by dissolution in triple-distilled and deionized water and then was further diluted with the same solvent to appropriate concentration. 0.04 M Britton-Robinson (B-R) buffer (pH 7.4) was prepared from H_3BO_3, H_3PO_4 and CH_3COOH solutions and also adjusted to the desired pH values with 0.1 M NaOH solution.

2.3. Synthesis of the Cu(II) complex

A $CuCl_2$ solution (0.5 mmol) in ethanol-water mixture (1:1) (25 mL) was added to a solution of NaOXA (1.0 mmol, 0.0423 g) in the same solvent (50 mL) in the mole ratio 1:2 (Cu(II):OXA^-). The mixture was stirred for 6 h at about 40 °C and then was left for about 2 weeks at room temperature. The light blue solid products were collected and washed several times with EtOH and dried at room temperature. Elemental analyses results of the complex (C% / H% / N%; found (calculated): 50.28 (49.70) / 4.88 (4.61) / 8.85 (9.15)) agree satisfactorily with the formulation $Cu(OXA_{hyd.})_2 \cdot H_2O$ where $OXA_{hyd.}$denotes to the hydrated form of OXA^- anion.

2.4. Synthesis of the Co(II) complex

A $CoCl_2$ solution (1 mmol) in ethanol-water mixture (1:1) (25 mL) was added to a solution of NaOXA (1.0 mmol, 0.0423 g) in the same solvent (50 mL) in the mole ratio 1:1 (Co(II):OXA^-).This mixture was also stirred for 6 h at about 40 °C. Then, the mixture was left for about 2 weeks at room temperature. The purple solid yields were obtained and were washed several times with EtOH and dried at room temperature. Elemental analyses results of this complex (C% / H% / N%; found (calculated): 43.54 (42.99) / 4.25 (4.18) / 7.48 (7.92)) agree satisfactorily with the formulation $Co(OXA_{hyd.})Cl(H_2O)$.

2.5. Computational procedure

Calculations were performed using Gaussian 09 [35], Gaussview 5.0 [36] and Spartan 08 [37]. Conformational analyses were performed by using the MMFF force field in Spartan08 to obtain initial structures. For further calculations, Density Functional Theory (DFT) approach was used [38]. Calculations were performed with the hybrid B3LYP functional (Becke's three-parameter nonlocal exchange functional [39, 40], Lee-Yang-Parr's correlation function [41]) using the 6-31G(d,p) basis set. All investigated structures were optimized in gas phase and in water. All optimized geometries have positive frequencies in both media showing that they correspond to minima. The most stable conformer for each molecule was determined and used in calculations.

To mimic the aqueous environment in experimental studies and to observe the solvent effect, Polarizable Continuum Model (PCM) [42, 43] was used in DFT calculations.

3. RESULTS AND DISCUSSION

3.1. Voltammetric behaviour of OXA^- in the absence and presence of Cu(II) or Co(II) ions

First of all, the SW voltammogram of OXA^- in the absence of metal ions (Cu(II) and Co(II)) was obtained at B-R buffer (pH 7.40) (Fig.1). As can be seen in Fig.1, OXA^- gave two-cathodic peaks at -0.180 V (1U) and -1.105 V (2U, main peak), respectively. The voltammetric behaviour of OXA^- in phosphate buffer of pH 7.0 had already been reported by Biçer and Coşkun [44]. Therefore, these

peaks (Fig. 1) can be attributed to the adsorption of OXA^- on the mercury electrode and the reduction of the heterocyclic isoxazole ring of OXA^- (main peak), respectively.

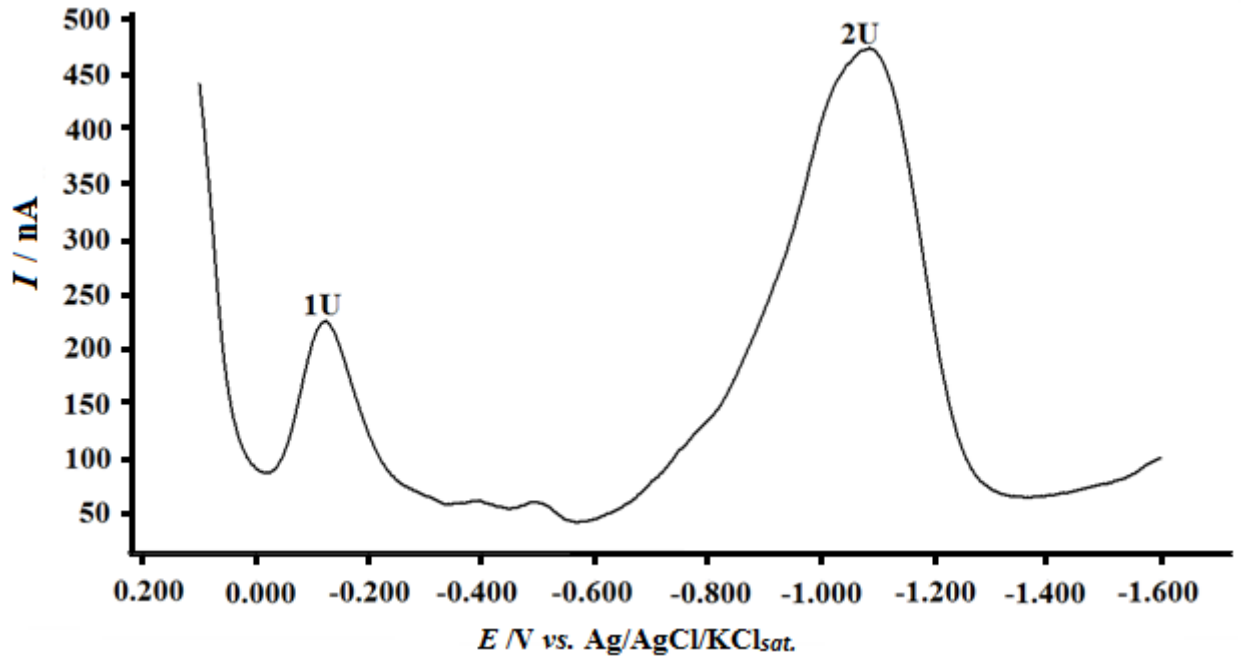


Figure 1. SW voltammogram of 4.0×10^{-5} M OXA^- in B-R buffer of pH 7.4 (Experimental conditions: scan rate, 200 mVs^{-1}; drop size, medium and equilibrium time, 5 s). 1U: the adsorption peak of OXA^-, 2U: the reduction of heterocyclic isoxazole ring of OXA^-.

The interaction of Cu(II) ions with OXA^- at physiological pH 7.4 in B-R buffer has been investigated by using SWV technique. According to Fig. 2, free Cu(II) ions gives a reduction peak at -0.152 V (1U) in the absence of OXA^-. With the addition of OXA^- to the Cu(II) solution, Cu(II)-OXA complex was recognized by a cathodic peak at -0.692 V (Fig. 2, 3U). The peak current of Cu(II)-OXA complex gradually increased by increasing OXA^- concentration. In addition, the currents of OXA^- reduction peaks increased with increasing its concentration (Fig. 2, 2U and 4U). Already, it is well known that the Cu(II) complexes of some β-lactam antibiotics (benzylpenicillin, amoxycillin, ampicillin, phenoxymethylpenicillin) reduce at more negative potentials than those of free Cu(II) reduction (Cu(II)/Cu) [45].

The SW voltammogram of 1.0×10^{-4} M $CoCl_2$ in the absence of ligand, gives one peak at -1.264 V due to the reduction of free Co(II) (Fig. 3a). After adding OXA^- into the cell containing 1.0×10^{-4} M Co(II), the new cathodic peak at -1.440 V is observed (Fig. 3b-e). With increasing OXA^- concentration, the current of the peak at -1.440 V increases due to the complex formation between Co(II) and OXA^- (Fig. 3b-e). On the other hand, in the presence of OXA^-, the reduction peak current of free Co(II) at -1.264 V is smaller than its current in the absence of OXA^-. The last case also supports the complexation OXA^- with Co(II) ions.

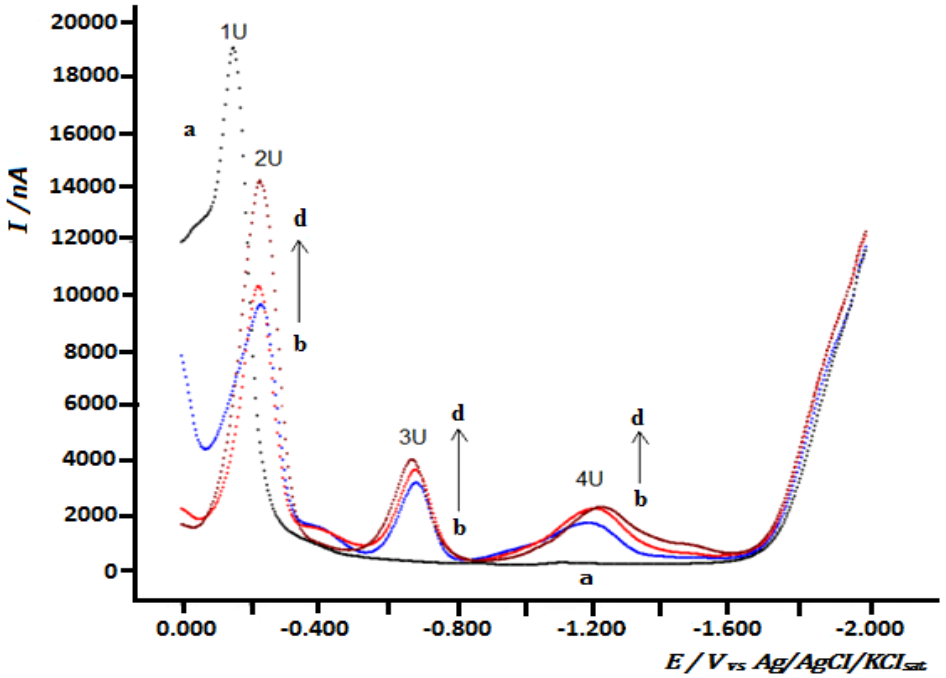


Figure 2. SW voltammograms of a) 1.0×10^{-4} M Cu(II) (1U), b) 1.0×10^{-4} M Cu(II) + 6.0×10^{-5} M OXA^-, c) 1.0×10^{-4} M Cu(II) + 1.6×10^{-4} M OXA^-, d) 1.0×10^{-4} M Cu(II) + 3.0×10^{-4} M OXA^- in B-R buffer pH 7.4 (*Experimental conditions as in Fig. 1.*). 1U: the reduction of free Cu(II) ions, 2U: adsorption peak of OXA^-, 3U: the reduction of the Cu(II) complex, 4U: reduction of heterocyclic isoxazole ring of OXA^-.

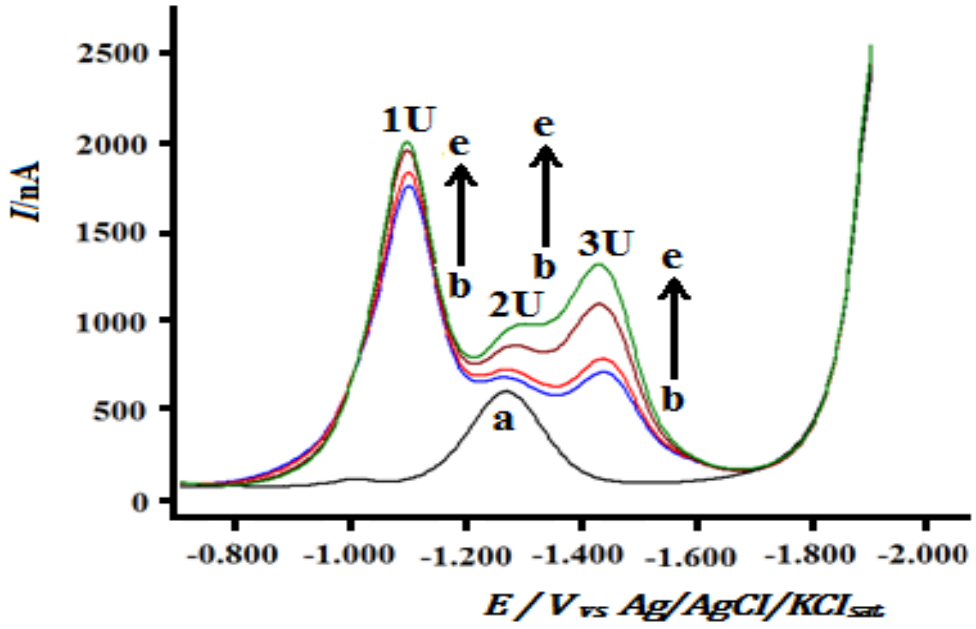


Figure 3. SW voltammograms of a) 1.0×10^{-4} M Co(II) (3U), b) 1.0×10^{-4} M Co(II) + 1.2×10^{-4} M OXA^-, c) 1.0×10^{-4} M Co(II) + 1.4×10^{-4} M OXA^-, d) 1.0×10^{-4} M Co(II) + 1.8×10^{-4} M OXA^-, e) 1.0×10^{-4} M Co(II) + 2.0×10^{-4} M OXA^- in B-R buffer pH 7.4 (*Experimental conditions as in Fig. 1.*). 1U: reduction of heterocyclic isoxazol ring of OXA^-, 2U: free Co(II) reduction peak, 3U: the reduction of the Co(II) complex.

When reduction potentials of the OXA complexes are compared with each other, it can be observed that the peak potentials of the Cu(II) and Co(II) complexes are -0.692 V and -1.440 V, respectively. This situation shows that the reduction of Cu(II) complexes is easier than Co(II)-OXA complex.

Complex formation constants are determined by using SWV measurements. The formation constants and stoichiometries of Cu(II) and Co(II) complexes were calculated by the Deford-Hume method [46]. It was found that the metal to ligand mole ratio was 1:2 for the Cu(II) complex and 1:1 for the Co(II) complex [47]. The formation constants (*K*) of the Cu(II) and Co(II) complexes were determined as 3.98×10^4 (log K = 4.60) and 2.57×10^4 (log K = 4.41), respectively [47]. Consequently, Cu(II) complex has higher formation constant. This case can be probably sourced from the number of OXA bound to the metal ion. Moreover, the stability order of these complexes obeys the Irving-Williams stability series as in the complexes of other *β*-lactam antibiotics in the literature [48].

In a previous paper [45], it was concluded that firstly Cu(II)(penicillin)$_2$ was formed and then it was transformed to Cu(II)(penicilloic acid)$_2$ in aqueous medium due to the catalytic hydrolysis of *β*-lactam ring in the presence of Cu(II) ions. Therefore, it was thought that OXA^- would give the hydrolysis reaction in the presence of Cu(II) and Co(II) ions as similar manner to those mentioned in the literature [45].

3.2. FT-IR spectra of the synthesized Cu(II) and Co(II) complexes

IR spectra of NaOXA and the synthesized solid complexes of Cu(II) and Co(II) ions with OXA^- have also been investigated. OXA^- has various potential donor sites. The IR spectrum of NaOXA reveals bands at 1607 and 1420 cm^{-1} due to ν_{asym}(COO) and ν_{sym}(COO). The C=O stretching in the *β*-lactam in OXA appears as a strong band at 1764 cm^{-1} (Fig. 4).

The comparison of the IR spectrum of NaOXA with the spectra of Cu(II) and Co(II) complexes provides evidence regarding both the bonding sites and the hydrolysis of OXA^- (Fig. 5) at the synthesis stage of the complexes. The hydrolysis of OXA^- (Fig. 5) can be given in a similar manner to the hydrolysis of penicillins in the presence of Cu(II) [45].

It is well known that the IR spectra of *β*-lactam substrates give a strong band for the *β*-lactam C=O stretching vibration, which gradually disappears on hydrolysis [45, 49]. The band at 1764 cm^{-1} related to the C=O vibration of *β*–lactam group is practically absent in the spectra of the Cu(II) and Co(II) complexes. Instead of this band, the very weak bands at 1747 and 1739 cm^{-1} at the Cu(II) and Co(II) complexes were obtained. In addition to the disappearance of the band at 1764 cm^{-1}, the appearance of the new and strong bands at 1654 and 1640 cm^{-1} for the Cu(II) and Co(II) complexes corresponding to the carboxylate in the ring-opened product ($OXA_{hyd.}$) were also observed (Fig. 4).

Moreover, the C-N vibration band at 1340 cm^{-1} in the *β*–lactam ring of NaOXA that is not only shifted to 1321 and 1267 cm^{-1}, but also decreased in intensity as a result of the complexation of the ligand with Co(II) and Cu(II) ions (Fig. 4). This observation may source from the coordination through the nitrogen atom at the hydrolysed structure of OXA^- (Fig. 6).

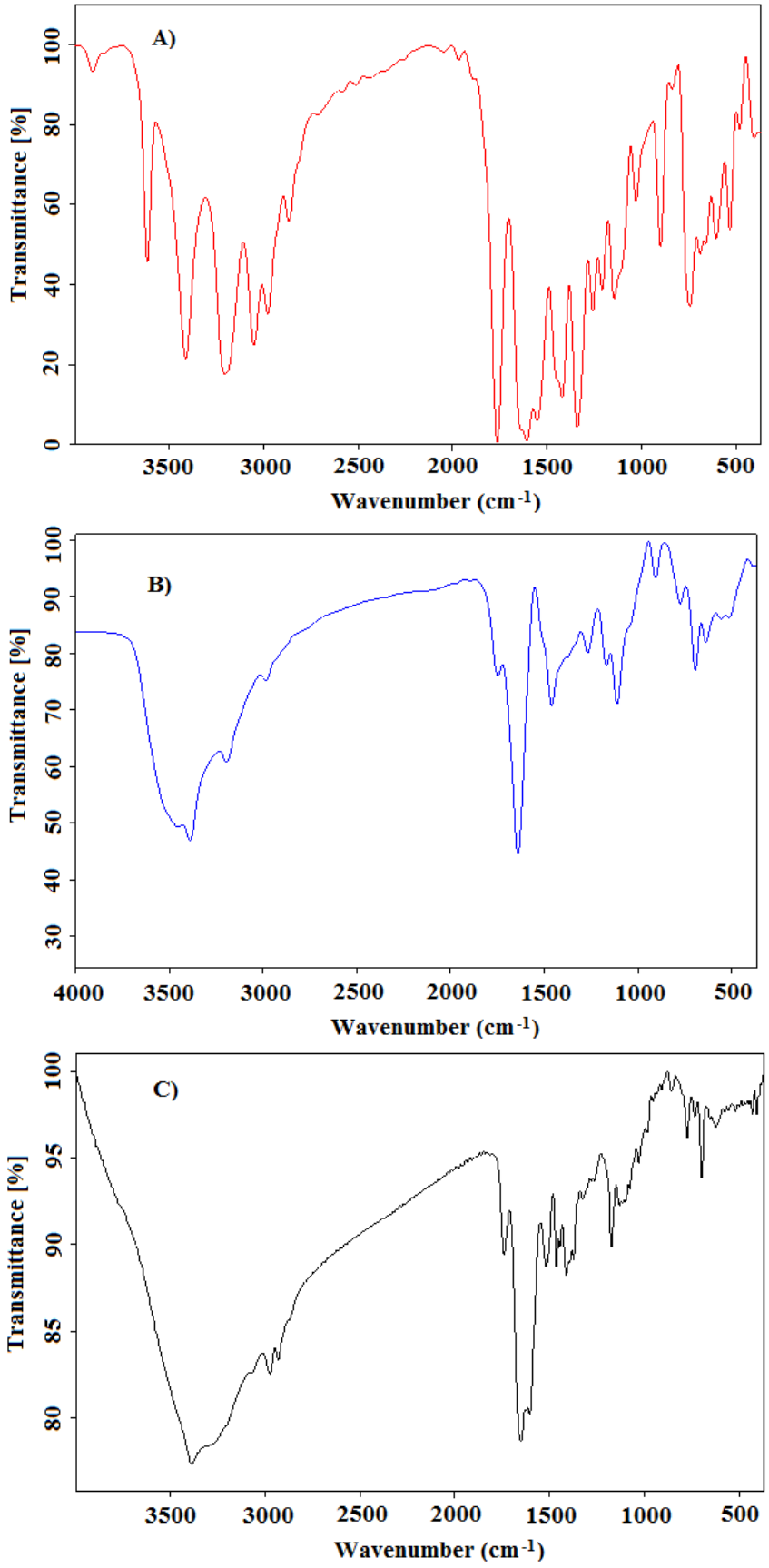


Figure 4. FT-IR spectra of **A)** NaOXA, **B)** $Cu(OXA_{hyd.})_2 \cdot H_2O$ and **C)** $Co(OXA_{hyd.})Cl(H_2O)$.

The carboxylate bands (1607 and 1420 cm^{-1}) of NaOXA shift to 1516 (the Co(II) complex) and 1457/1460 cm^{-1} (the Co(II)/Cu(II) complexes) owing to the complex formation. This case may be an evidence for binding of carboxylate oxygen atom to the metal ions (Fig. 6).

The broad absorption band centred at about 3390 cm^{-1} in the spectra of the Cu(II) and Co(II) complexes can be attributed to the presence of water in the complex structures. In a previous study [50], the complex structure of dicluxacillin which contains the *β*–lactam ring with Co(II) ions, the coordination of Cl^- ion and water molecules was also indicated.

Finally, the proposed chemical structures of the complexes of Cu(II) and Co(II) with $OXA_{hyd.}^-$ can be given as shown in Fig. 6.

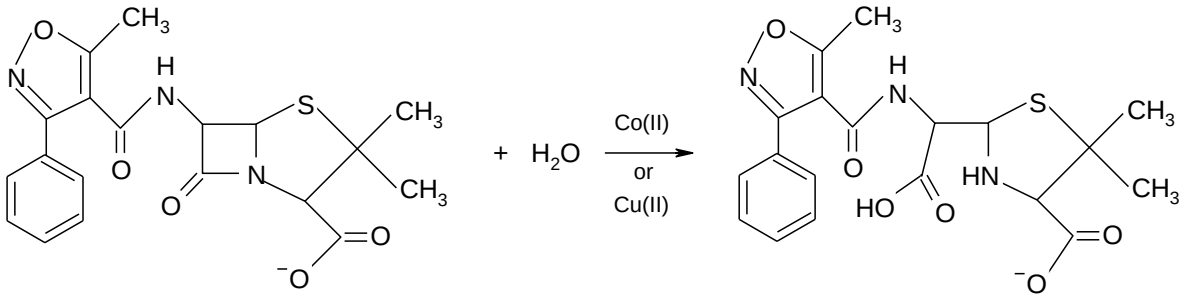
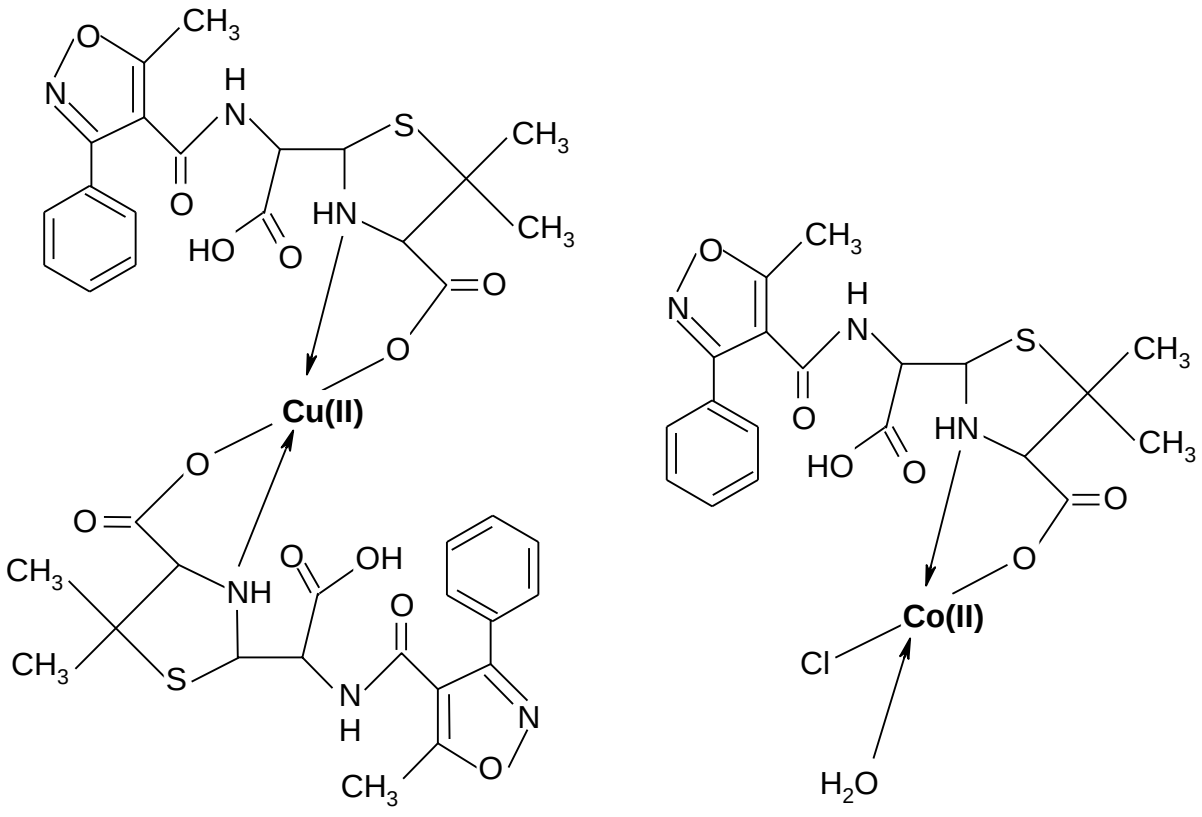


Figure 5. The hydrolysis of OXA^- in the presence of Co(II) or Cu(II) ions.



(A) **(B)**

Figure 6. Suggested structural formula of **A)** $Cu(OXA_{hyd.})_2$ and **B)** $Co(OXA_{hyd.})Cl(H_2O)$ complexes.

3.3. DFT analysis of investigated systems

Firstly, the structures for the hydrolysis of OXA^- were investigated. A total of 71 structures for OXA^- and 40 structures for its hydrolysed form OXA_{hyd}^- obtained from conformational analyses were optimized and the most stable conformers were determined (Fig. 7). As seen in the figure, the distances between the two terminals of the OXA^- and its hydrolysed form, OXA_{hyd}^-, increase in water which makes the hydrolysis and the interactions with metal ions much easier.

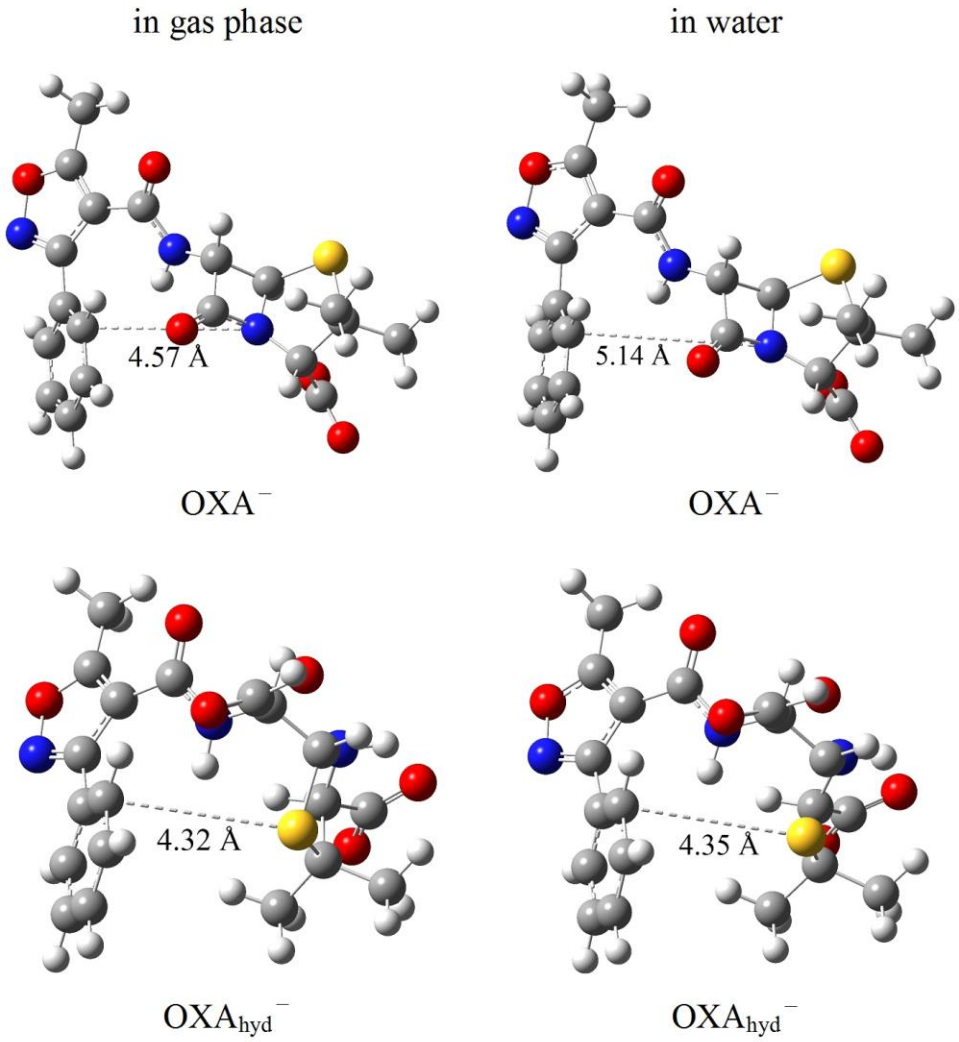


Figure 7. Structures of OXA^- and its hydrolysed form (OXA_{hyd}^-) in gas phase and in water optimized at B3LYP/6-31G(d,p) level.

Fig. 8 displays the most stable Co(II) and Cu(II) complexes of OXA_{hyd}^-. All possible binding sites were investigated for Co(II) complex and only two complex structures were obtained. As seen from the structures, Co(II) binds to three centres in gas phase: O1, O2 and N1. However, due to the presence of electrostatic interactions in PCM model (interactions with H_2O molecules in the real

system), it only binds to two centres O2 and N1. This prediction is in agreement with the experimentally suggested structure.

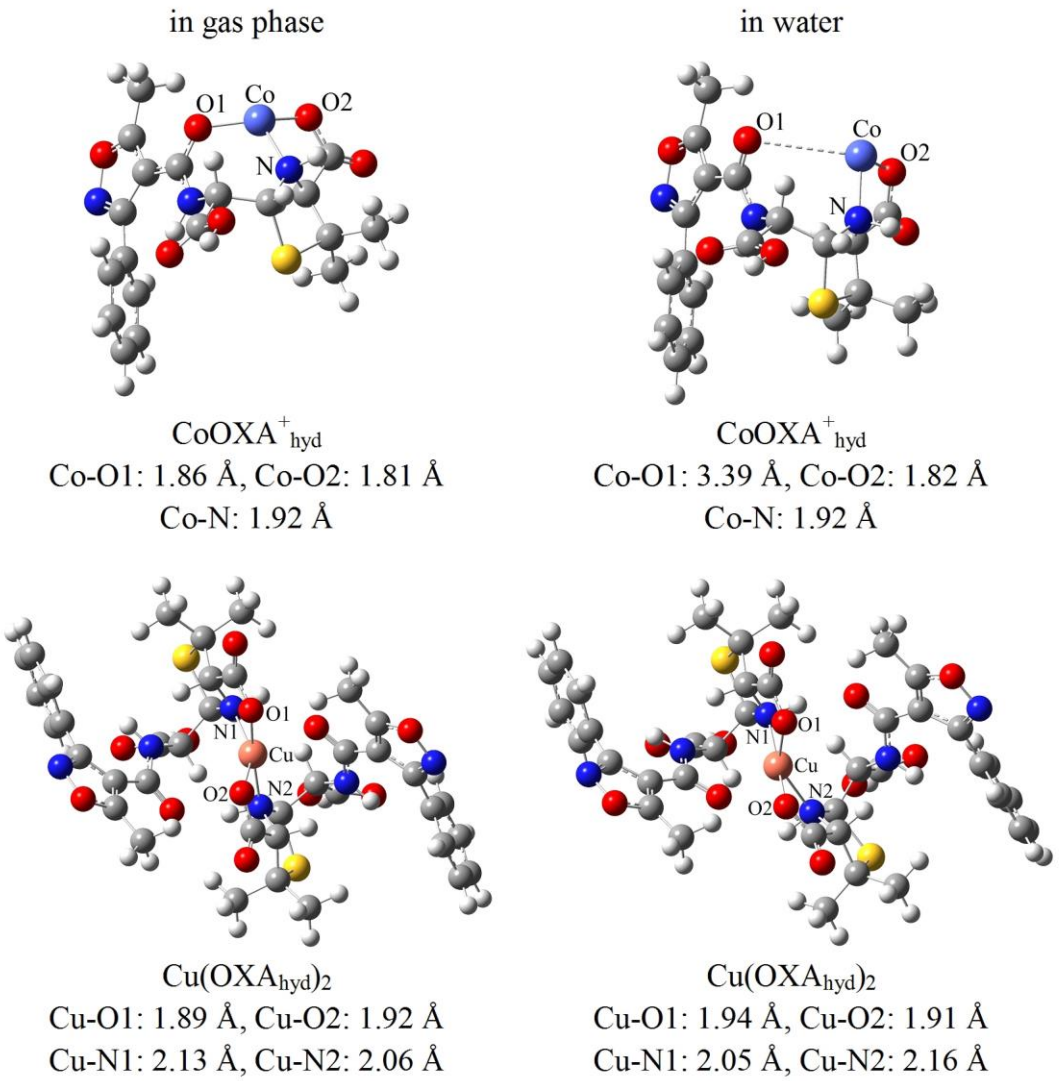


Figure 8. Structures of $Co(OXA_{hyd})^+$ and $Cu(OXA_{hyd})_2$ in gas phase and in water optimized at B3LYP/6-31G(d,p) level.

For Cu(II) complexes, only dimers were investigated to compare the data with the experimental results. We have constructed seven different conformers and the most stable $Cu(OXA_{hyd.})_2$ complexes in gas phase and in water are given in Fig. 8. The optimized structures revealed that Cu(II) binds to one of the carboxyl oxygens on each OXA_{hyd}^- monomer and is coordinated towards the thiazolidine ring nitrogens with a symmetrical orientation. This structure also agrees well with the experimental prediction.

Table 1 summarizes the calculated dipole moments (μ, Debye), sum of electronic and zero point energies (E_{elec}+ZPE, Hartree), complexation energies (ΔE_C) and solution-gas phase energy differences (ΔE_S) of studied systems in gas phase and in water (ε = 78.4) at B3LYP/6-31G(d,p) level.

Table 1. Dipole moments (μ, Debye), sum of electronic and zero point energies (E_{elec}+ZPE, Hartree), complexation energies (ΔE_C) and solution-gas phase energy differences (ΔE_S) of complexes in gas phase and in water, ε = 78.4, calculated at B3LYP/6-31G(d,p) level.

	μ (D)	**E_{elec}+ZPE (Hartree)**	**ΔE_C (kcal/mol)**	**ΔE_S[d] (kcal/mol)**
in gas phase				
OXA^-	11.94	-1673.136426		
H_2O	2.04	-76.398367		
OXA_{hyd}^-	13.12	-1749.573948	-24.6[a]	
$Co(OXA_{hyd.})^+$	6.22	-3131.956255		
Co(II)		-1381.516184	-543.5[b]	
$Cu(OXA_{hyd.})_2$	12.51	-5139.414779		
Cu(II)		-1639.213084	-661.3[c]	
in water				
OXA^-	16.67	-1673.227541		-57.2
H_2O	2.26	-76.405409		-4.4
OXA_{hyd}^-	16.29	-1749.665289	-20.3[a]	-57.3
$Co(OXA_{hyd.})^+$	16.61	-3132.031078		-47.0
Co(II)		-1382.178945	-117.2[b]	-415.9
$Cu(OXA_{hyd.})_2$	18.97	-5139.463368		30.5
Cu(II)		-1639.756714	-236.0[c]	-341.1

[a] $\Delta E_C = E_{Complex} - (E_{OXA}^- + E_{H2O})$
[b] $\Delta E_C = E_{Complex} - (E_{OXAhyd}^- + E_{Co(II)})$
[c] $\Delta E_C = E_{Complex} - (2E_{OXAhyd}^- + E_{Cu(II)})$
[d] $\Delta E_S = E_S - E_G$

The results show that all studied systems have high dipole moments; thus, they are highly stabilized in water indicated by large negative values for ΔE_S. The significant changes are observed for the metal ions due to their charges. The ΔE_C values display that the formed complexes are highly stable in both media. As can be seen in Table 1, the sums of electronic and zero point energies of OXA_{hyd}^- are higher negative values than those of OXA^- in both gas phase and water. This is the

expected result of the hydrolysis process. The similar case was obtained for the hydrolysis of *cis*- and *trans*-3,4-dimethyl-5-phenyloxazolidines [51].

Computational IR spectra of OXA_{hyd}^-, $Co(OXA_{hyd})^+$ and $Cu(OXA_{hyd})_2$ molecules are given in Fig. 9. It is clearly seen that new peaks and shifts in the peaks appear upon binding of Co(II) and Cu(II) to OXA_{hyd}^-.

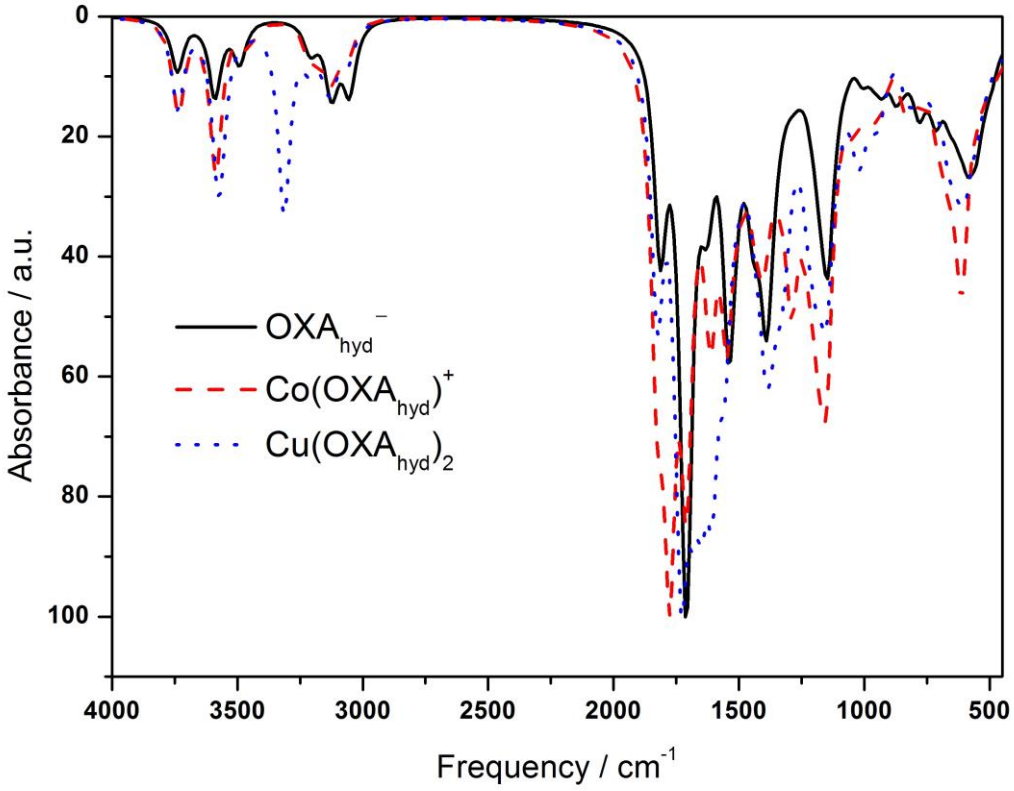


Figure 9. Calculated IR spectra of OXA_{hyd}^-, $Co(OXA_{hyd})^+$ and $Cu(OXA_{hyd})_2$ molecules in water at B3LYP/6-31G(d,p) level.

4. CONCLUSION

In the present study, the voltammetric and spectroscopic behaviours of the complexes of OXA^- with Cu(II) and Co(II) metal ions have been studied. From voltammetric data, the stability constants and stoichiometries of these complexes were determined at physiological pH. It was seen that the reduction of the Cu(II) complex was easier than that of the Co(II)-OXA complex. According to the IR data, it was verified that OXA^- was hydrolysed at the synthesis stage of the metal complexes in aqueous medium. Density functional calculations at B3LYP/6-31G(d,p) level support the experimental conclusions.

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