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Redox behavior of aliphatic hydroxamic acid and its iron(III) complexes

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ABSTRACT

N-Hydroxydodecanamide (HA12) and its trihydroxamato-iron(III) complex (HA12Fe3) have been synthesized and characterized by various methods including structural determination by single crystal X-ray diffraction and cyclic voltammetry (CV). In order to complete our previous CV study on HA12 and its complexes, our aim was to investigate the variation in redox potential upon changes in concentration and pH. The redox couples previously observed with HA12 and HA12Fe3 at 100 µM shifts towards less positive values when the concentration or pH of the solution increases. These results indicate that oxidation is easier when concentrations are higher and in basic media. The slopes of -0.06 V/pH (in agreement with the theoretical data) and -0.077 V/pH (slightly higher than the theoretical slope) were observed for HA12 and HA12Fe3, respectively. This observation would explain the slower oxidation of HA12Fe3 than HA12.

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1. Introduction

Hydroxamic acid (HA) with the general formula: R(CO)(NH)OH are a particularly interesting class of bidentate organic *O*,*O*-donor ligands and have many different applications, mainly in drug design and analytical chemistry [1]. Electrochemical studies have been carried out with certain HA and their derivatives to explore the oxidoreductive reaction mechanism at different pH. They can indicate the nature of the products and the number of electrons involved in the redox process [2-5].

The oxidation of certain HA (R(CO)(NH)OH, R = CH_3, C_6H_5, $C_6H_5CH_2$) has been studied on platinum electrodes in a buffered aqueous solution at different pH values. The voltammetric data showed that in acidic media, HA dissociation precedes the quasi-reversible charge transfer step and a two-electron oxidation process leads to carboxylic acids as end products. On the other hand, in alkaline media, the reaction mechanism involving the formation of transient radical anions was demonstrated [2]. In another example, the electrochemical properties of *N*-phenylcinnamohydroxamic acid (PCHA) were examined by cyclic voltammetry (CV). Its redox behavior in acetonitrile showed an electron transfer process followed by a chemical reaction. Furthermore, its electrochemical property in an aqueous sodium acetate solution (0.25 M) was found to be a function of pH [3]. The results showed anodic and cathodic peaks that shifted towards the negative potential with increasing pH to 9. The CV data of PCHA were also studied in the presence of iron(III) ions [3].

The CV study of Fe(III) complexes of alanine-, serine-, lysine-, histidine- and glutamo-γ-hydroxamic acid has been investigated on suspended mercury drop electrodes. The aim was to determine the mechanism involved in the electron transfer processes and to gain insight into the influence of ligands on the redox potential. A comparison of the redox potential with the redox potentials of certain natural hydroxamates identified as siderophores was discussed [4].

Kinetic studies of the hydrolysis of formo-(HA1) and aceto-(HA2) hydroxamic acids alone and the presence of plutonium(IV) ions were carried out. The slow reduction of Pu(IV) hydroxamate complexes to Pu(III) aquo ions was characterized by UV/Vis spectrophotometry and CV. The Pu(IV) reductions in the presence of HA1 and HA2 are consistent with a mechanism in which the free HA in solution is hydrolyzed while the Pu(IV) ions remain fully complexed to the hydroxamate ligands while, close to a 1:1 Pu(IV):HA ratio, some of the free Pu(IV) ions are released from the complex and the reduction begins [5].

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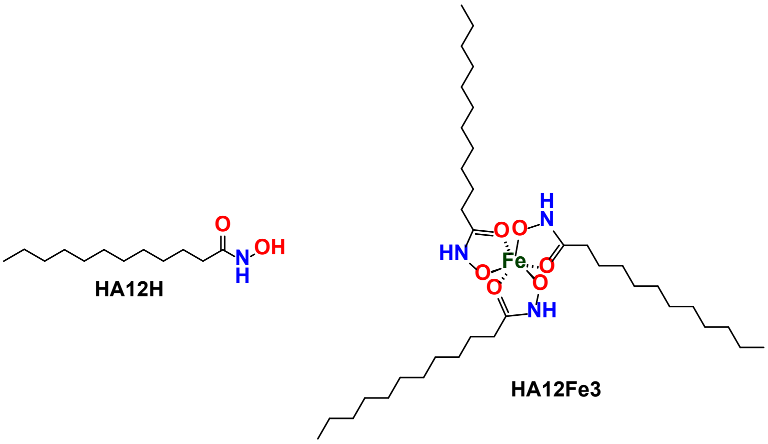


Figure 1. Chemical structures of *N*-hydroxydodecanamide (HA12) and tri-dodecanohydroxamato-Fe(III) (HA12Fe3).

The work by Alemu and Chandravanshi only reported the effect of pH on the displacement of PCHA oxidation and reduction peaks [3]. Comparatively, in our previous work, the CV of HA and Fe(II/III) complexes revealed a reversible and a quasi-reversible redox process, respectively [6]. Numerous complexes with HA have been reported, such as the tris-chelate complex of Fe(III) with aceto-HA [7] and a similar complex with heptano- and octano-HA [8]. However, their electrochemical properties have not been studied by varying the reaction media and concentration. In view of these findings on the electrochemical studies of HA and its derivatives, we wanted to fill these gaps, and further studies were undertaken to determine the redox process behind these data by varying the conditions (concentration and pH of the medium).

Our group has shown the selective biological properties of HA12 against *Candida albicans* and the HA12Fe3 complex against *Mycobacterium smegmatis* [6]. Furthermore, the CV study carried out with these compounds showed that redox processes occur. These could lead to the formation of ionic, radical or molecular species that could be at the origin of biological activity. With a view to have an insight into the putative mechanism of action of these compounds on microorganisms, we investigated HA12 and its corresponding Fe(III) complex HA12Fe3 (Figure 1) by CV at various concentrations and pH.

2. Experimental

2.1. Materials

MeOH was obtained from Sigma-Aldrich (Saint Louis, USA). Sodium hydroxide, potassium hydroxide and sodium acetate were purchased from Merck (Darmstadt, Germany). Potassium chloride was obtained from Panreac (Barcelona, Spain). The carbon-screen-printed electrode (cSPE) was purchased from DropSens (Asturias, Spain). Sodium dihydrogen phosphate and monohydrogen phosphate were obtained from Acros Organics (New Jersey, USA). The ammonium formate and pH meter were purchased from Metrohm (Antwerpen, Belgium). CV experiments were performed with an Epsilon potentiostat BASi (West Lafayette, USA) connected to a cSPE (DRP-110). The cSPE, constituted of a miniaturized cell with 3 electrodes all in one, includes a carbon working electrode, a carbon counter electrode and a silver pseudo reference electrode (Ag/AgCl). The Epsilon-EC-version 1.50.69_XP was used for instrument control. Acetic acid was obtained from VWR (Fontenay-Sous-Bois, France), and formic acid was purchased from UCB (Drogenbos, Belgium).

2.2. Methods

The synthetic method for HA12 and HA12Fe3 and their preliminary characterization by CV were reported in previous work [6]. Briefly, in the study, CV was carried out in single and multiple sweeps (10 cycles) at a speed of 50 mV/s. The samples were dissolved in MeOH to give a concentration of 10 mM. Subsequently, these solutions were diluted with an aqueous solution of KCl (1 M) in 5% MeOH to final concentrations of 100, 250, 500, and 1000 µM, respectively. Next, four aqueous solutions of NaH_2PO_4, Na_2HPO_4, CH_3COONa, and $HCOONH_4$ each containing KCl (1 M) were prepared at a concentration of 0.1 M in a final volume of 100 mL. Subsequently, buffer solutions of $H_2PO_4^-/HPO_4^{2-}$ (pH = 7.4), CH_3COOH/CH_3COO^- (pH = 4.5) and $HCOOH/HCOO^-$ (pH = 2.5 and 3.5) were obtained after adding solutions of Na_2HPO_4 (0.1 M), CH_3COOH (17.32 M) and HCOOH (26.5 M), respectively, to solutions of NaH_2PO_4 (0.1 M), CH_3COONa (0.1 M) and $HCOONH_4$ (0.1 M). After preparing these four buffered solutions, adjustments were made using a pH meter and MeOH was added to obtain a final volume of 100 mL of these buffers and a methanolic concentration of 5%. HA12 and HA12Fe3 were dissolved in MeOH to obtain a 10 mM solution and diluted with four 0.1 M buffer solutions (with 1 M KCl and 5% MeOH) to obtain a final sample concentration of 250 µM. Thus, 50 µL of HA12 or HA12Fe3 solution at the chosen concentrations were deposited on the cSPE electrode in order to determine the influence of the concentration and pH of the media on the electrochemical process observed with these two compounds.

3. Results and discussion

3.1. Potential variation as a function of concentration

Graphs expressing intensity as a function of the potential for the compounds HA12 and HA12Fe3 in aqueous solution with KCl (1 M) and 5% MeOH at concentrations of 100 µM showed quasi-reversible processes in previously work [6]. In the CV obtained at concentrations of 100 µM [6], 250, and 500 µM with a sensitivity of 100 µA, a slight shift towards less positive potentials is observed without any significant change in the electrochemical processes. However, at a concentration of 1000 µM, saturation was observed on the voltammogram with the same sensitivity (Figures 2 and 3). After varying the sensitivity from 100 µA to 1 mA, only the reduction peaks showed this saturation phenomenon at 1000 µM (Figure 2). On the CV obtained for HA12 (Figure 2), only the oxidation peaks are clearly observable at +0.18 V. Their reduction peaks could be located at -0.12 V (HA12).

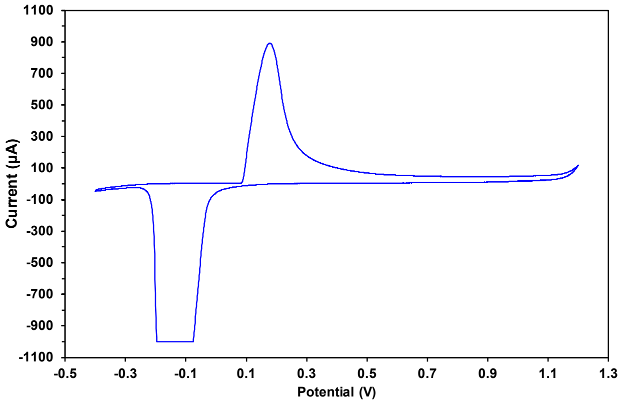


Figure 2. CV obtained for compound HA12 at a concentration of 1000 µM in an aqueous solution of 1 M KCl with 5% MeOH with a scale of 1 mA.

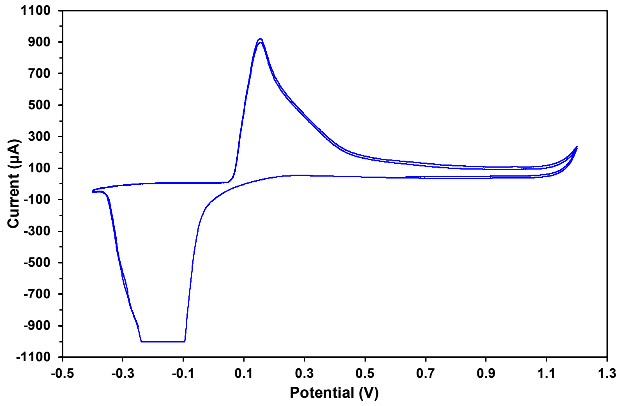


Figure 3. CV obtained for compound HA12Fe3 at a concentration of 1000 µM in an aqueous solution of 1 M KCl with 5% MeOH with a scale of 1 mA.

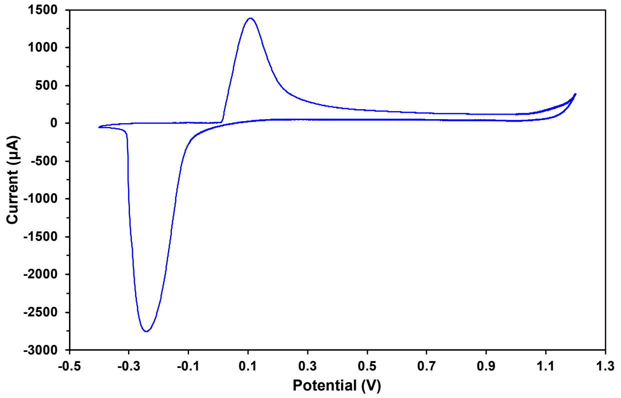


Figure 4. CV obtained for compound HA12 at a concentration of 1000 µM in an aqueous solution of 1 M KCl with 5% MeOH with a scale of up to 10 mA.

The same results obtained with compound HA12 were also observed with its corresponding complex (HA12Fe3), after varying the sensitivity from 100 µA to 1 mA. The reduction peaks showed this saturation phenomenon at 1000 µM (Figure 3). On the CV obtained for the complex HA12Fe3 (Figure 3), only the oxidation peaks are clearly observable at +0.18 V. Their reduction peaks could be located at -0.17 V (HA12Fe3). However, at 10 mA sensitivity (Figure 4), the oxidation and reduction peaks shifted towards the less positive values (+0.15 V and -0.24 V, respectively) for compound HA12. Regarding the complex HA12Fe3 (Figure 5), the potential values remained unchanged. We can conclude from these results that increasing the concentration of compounds influences the redox process. The redox couples previously observed with compound HA12 at 100 µM at values of +0.39 V and -0.19 V [6], shift towards less positive values (easier oxidation) when the concentration increases to 1000 µM (Figures 4 and 5).

3.2. Potential variation as a function of pH

The cyclic voltammograms plotted against pH for the oxidation peaks observed in the different buffer solutions used in the presence of aqueous KCl (1 M) and 5% MeOH show slopes of -0.06 V/pH (Figure 6a) and -0.077 V/pH (Figure 6b), respectively, for the compounds HA12 and HA12Fe3 at 250 µM. The potential of the redox couples moves toward the less positive values when the pH of the solution increases. This indicates that oxidation is easier when the solutions are less acidic.

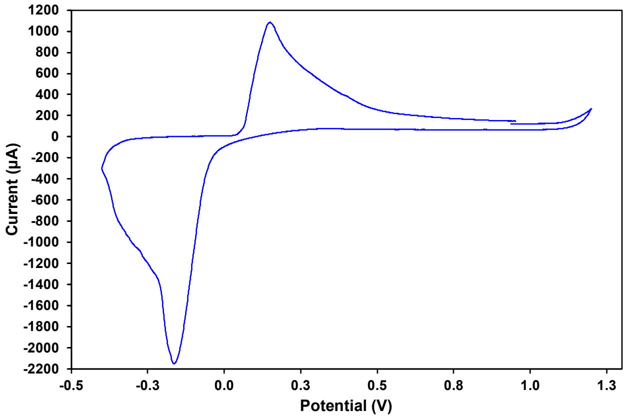
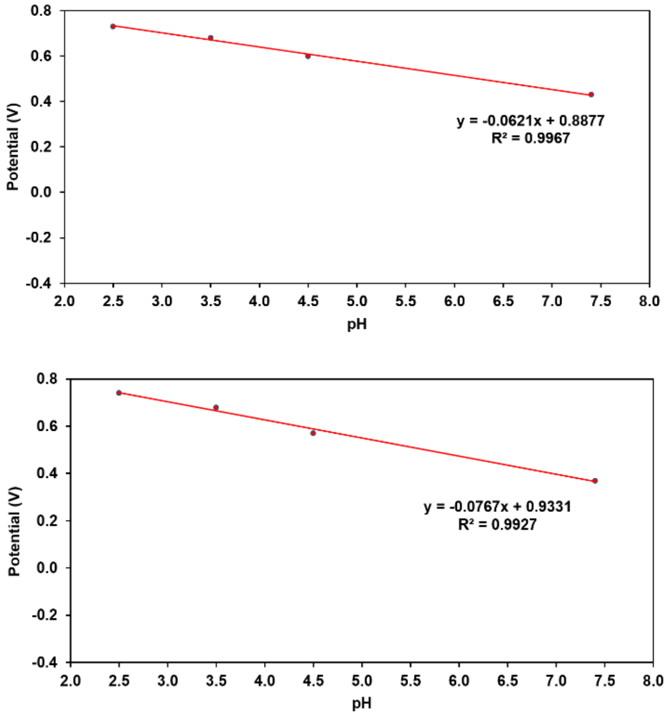


Figure 5. CV obtained for compound HA12Fe3 at a concentration of 1000 µM in an aqueous solution of 1 M KCl with 5% MeOH with a scale of up to 10 mA.



(a)

(b)

Figure 6. Potentials obtained for compounds HA12 (a) and HA12Fe3 (b) at a concentration of 250 µM in different buffer solutions with aqueous KCl (1 M) and 5% MeOH.

The study of the variation in the redox potential as a function of concentration and pH showed that the electrochemical processes observed with compounds HA12 and HA12Fe3 are influenced by these two parameters. We found that as the pH of the values of the solution increased, the redox potential of compound HA12 shifted toward a less positive potential with a slope of -0.06 V/pH. This slope is in agreement with the theoretical slope (2.303×n×R×T/2×F) of -0.059 V/pH with a number of protons n involved in the reaction equal to 2 (Equation 1) [9,10]. This result is in agreement with an easier oxidation of HA in less acidic solutions.

With complex HA12Fe3, although the redox potential values shifted towards less positive potentials as a function of pH, the slope obtained (-0.077 V/pH) was slightly higher than the theoretical -0.059 V/pH. This observation could explain the slower oxidation of Fe(II/III) complexes than that of HA. These slope values found with these two compounds (HA12 and HA12Fe3) correspond to a redox process with an exchange of 2 electrons and 2 protons (Equation 2) [9].

$$E_{ox/red} = E°_{ox/red}(pH = 0) - (2.303\frac{n×R×T}{2×F})\ pH \qquad (1)$$

$$Red \leftrightharpoons Ox + nH^+ + 2e^- \qquad (2)$$

where $E_{ox/red}$ = Potential (V) of the redox couple, $E°_{ox/red}$ = Standard potential (V) of the redox couple at pH = 0 ([H^+] = 1 M), but E° also depends on the medium (HCl is different from HNO_3, etc.), ox/red = Oxidizing/reducing couple, n = Number of protons involved in the reaction, R = Perfect gas constant (8.314 $J·K^{-1}·mol^{-1}$), T = Absolute temperature (K), and F = Faraday constant (96485 $C·mol^{-1}$).

Based on published studies on the oxidation pathways of HA and its complexes, compound HA12 could oxidize with either the formation of an intermediate acyl radical with loss of an electron, or the formation of a nitroso acyl, both hydrolyzing to their respective carboxylic acids ($CH_3(CH_2)_{10}COOH$, that is, lauric acid) [6,11]. Oxidation of the complex HA12Fe3 could generate the Fe(III) ion by decomplexation and lauric acid [6]. The reduction that could occur during the redox process of compound HA12 is the transformation of lauric acid into its amide form ($CH_3(CH_2)_{10}CONH_2$) [6,12]. As for complex HA12Fe3, its hydroxamate form could undergo the reduction process as for compound HA12. In addition, the Fe(III) ion could be reduced to Fe(II) (in the form of $Fe(OH)_2$ at high pH) and then to Fe(0) [6,13]. However Fe(0) is unlikely, but $Fe(OH)_2$ at a high pH value is possible.

The redox behavior of the Fe(III) complexes of the cyclic hydroxamate siderophores alcaligin and desferrioxamine E was investigated by CV [14]. At lower pH values, the redox potential for both complexes shifts positive, with a loss of voltammetric reversibility, which is interpreted to be the consequence of a secondary dissociation of Fe(II) from the reduced form of the complexes [14]. When comparing the slopes obtained with the compounds HA12 (Figure 6a) and HA12Fe3 (Figure 6b) with the theoretical slope -0.059 V/pH (Equation 1), in the case of the complex HA12Fe3, the slope obtained is slightly greater than the theoretical slope and can be explained by a loss of voltammetric reversibility of the complex resulting from the reduction of Fe(III) to Fe(II). These observations have been reported to be of biological importance, as they suggest the possibility of a reductive mechanism in microbial cells that use these siderophores to acquire iron [14]. In addition, it has been reported that the electrochemical behavior of Fe(III) hydroxamates is generally a quasi-reversible, pH-dependent process [15]. These results are in agreement with those obtained in our investigation, although we did not use the same scanning speed and concentration. The CV study carried out by Caetano *et al.* involved Fe(III) acetohydroxamate with a scan speed at 100 mV/s and a concentration of 1 mM. At pH = 7, the potential decreased by 0.06 V per pH unit [15,16]. We obtained results similar to those of Caetano *et al.* at pH = 7.5. On the other hand, the electrochemical study of HA showed an irreversible anodic reaction (two-electron process) under strongly alkaline conditions, in the presence of oxidants [15,16]. The reversible electrochemical process (anodic and cathodic) obtained with our two compounds (HA12 and HA12Fe3) could be explained by the less alkaline conditions and the absence of oxidants.

4. Conclusion

The study of the variation in the redox potential as a function of concentration and pH showed that the oxidation of compounds HA12 and HA12Fe3 is facilitated at higher pH and at higher concentration. In fact, at 100 µM in the previous result, the oxidation potential (E_a) was around +0.4 V for HA12 and HA12Fe3 [6]. At 1000 µM, E_a is +0.2 V. Furthermore, the oxidation of complex HA12Fe3 is slower than that of its corresponding hydroxamic acid (HA12). The slope values found with these two compounds correspond to a redox process with an exchange of 2 electrons and 2 protons [9]. In summary, as previously demonstrated [15,16], our results showed a decrease in the redox potential of 0.06 V per pH unit for HA12 and 0.077 V per pH unit for HA12Fe3 when the solution is less acidic.

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Disclosure statement DS

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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Conceptualization: Ibrahima Sory Sow; Methodology: Ibrahima Sory Sow, Marie Vandeput; Software: Ibrahima Sory Sow, Marie Vandeput; Validation: Marie Vandeput, Michel Gelbcke, François Dufrasne; Formal Analysis: Ibrahima Sory Sow, Marie Vandeput; Investigation: Ibrahima Sory Sow, Marie Vandeput; Resources: Ibrahima Sory Sow, François Dufrasne; Data Curation: Ibrahima Sory Sow, Marie Vandeput; Writing - Original Draft: Ibrahima Sory Sow; Writing - Review and Editing: Ibrahima Sory Sow, Marie Vandeput, François Dufrasne; Visualization: Marie Vandeput, François Dufrasne; Supervision: Marie Vandeput, Michel Gelbcke, François Dufrasne; Project Administration: Marie Vandeput, François Dufrasne.

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