



Synthesis and characterization of two new hydroxamic acids derivatives and their metal complexes. An investigation on the keto/enol, E/Z and hydroxamate/hydroximate forms



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ABSTRACT

2-phenylbenzimidazole-N-acetohydroxamic acid (**HL**¹), 2-phenylbenzimidazole-N-butanohydroxamic acid (**HL**²) and Ni(II), Cu(II), Zn(II) and Cd(II) metal complexes have been synthesized and characterized by elemental analyses, ¹H NMR, ¹³C NMR, FT-IR spectrometry, LC-MS (ESI⁺) and thermal analyses. The results of NMR spectra and theoretical calculations showed that the hydroxamic acids were in the *keto-E* and *keto-Z* conformations. The elemental analysis and thermal analysis indicated that M:L ratio of the complexes are 1:1 and the spectral analysis confirmed that hydroxamate groups are keto form in the Ni(II) and Zn(II) complexes of 2-phenylbenzimidazole-N-butanohydroxamic acid and enol form in the other complexes.

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1. Introduction

Hydroxamic acids, RC(O)NHOH, represent a wide spectrum of biologically active compounds with anti-cancer, hypotensive, anti-tuberculosis, anti-malarial and anti-fungal properties. They can act as potent and selective inhibitors of enzymes such as matrix metalloproteinases, peroxidases, ureases and histone deacetylases [1,2]. Their common inhibitory effect is most likely based on the strong interaction of the hydroxamate group with the metal ion in the active centre of the enzyme disrupting the activity of the enzyme [3]. For example, suberoylanilidehydroxamic acid (SAHA) has come into clinical trial phase as a highly promising anticancer drug [4,5]. Experimental and theoretical studies on the structures, biological activities and protonation equilibrium studies of hydroxamic acids, especially aromatic hydroxamic acids such as benzohydroxamic acid (BHA), salicylhydroxamic acid (SHA) and their metal complexes have received remarkable attention recently [4,6].

Hydroxamic acids are very interesting molecules because of

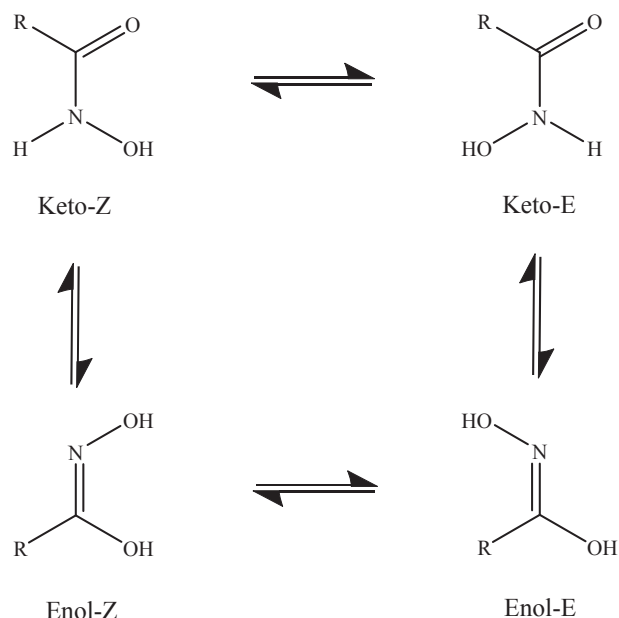
their tautomeric (*keto-enol*) and conformational (*E-Z*) structures. Theoretical calculations indicate that *keto-Z* structure is more stable than the *keto-E*, *Enol-Z* and *Enol-E* structures (Scheme 1) [6–11]. Most of the studies on E/Z conformation are related with formo-, aceto-, N-methylaceto- and benzohydroxamic acids [6–19]. Recently, a conformational study has been made on different hydroxamic acids [20]. Possible conformations can be monitored by NMR spectroscopy experimentally [6,14,20–22]. Some of the hydroxamic acids show two sets of ¹H singlets in the region 8.0–11.0 ppm, one set more intense than the other. The major peaks are assigned to *keto-Z* form and minor peaks *keto-E* form of the NH and OH protons of hydroxamic acids [22].

In the most of metal complexes of hydroxamic acids, ligands are keto form and coordination occurs through carbonyl oxygen and deprotonated OH group (O, O). Complexes of hydroxamic acids including enol form can be prepared under custom conditions (Scheme 2) [23–27].

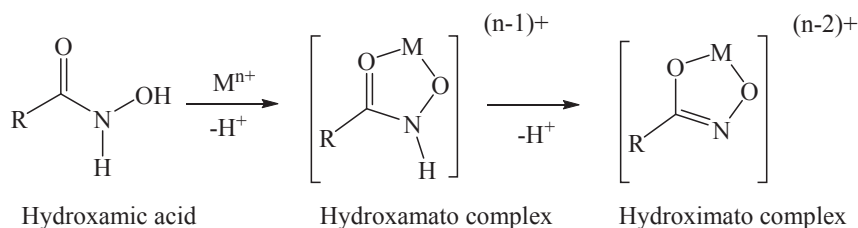
M:L ratio of M⁺² complexes is 1:2 generally ((RCONHO)₂M). When M:L ratio is 1:1, the coordination is completed by hydroxyl group and water molecules ((RCONHO)M(OH)) [28–30]. Rarely, some 1:1 complexes form by using enol configuration of the ligands and the product's formula is probably (RCONO)M [28].

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Scheme 1. Stable conformational and tautomeric forms of hydroxamic acids.



Scheme 2. Hydroxamic acid complexes in the different pH conditions.

In this work, we synthesized two hydroxamic acids that have different chain lengths and their Ni(II), Cu(II), Zn(II) and Cd(II) metal complexes. The new molecules were characterized by elemental analyses, ^1H NMR, ^{13}C NMR, FT-IR spectrometry, LC-MS (ESI $^+$) and thermal analyses. The conformations of the hydroxamic acid molecules were determined theoretically and experimentally.

2. Experimental

2.1. Materials and methods

All reactions were performed with commercially available reagents and they were used without further purification. ^1H NMR spectra were recorded with a Varian, 400 MHz spectrometer using Tetramethylsilane (TMS) as an internal standard. FT-IR spectra were recorded with a Perkin-Elmer Spectrum 100 with Universal ATR Polarization Accessory. Elemental analyses of the complexes (C, H and N) were determined with a LECO CHNS-932 analyzer. The TG and DTA curves were scanned using Seiko EXSTAR TG/DTG apparatus in a static air atmosphere (heating rate: $10\text{ }^\circ\text{C min}^{-1}$, platinum crucibles, mass: 5–10 mg and temperature range: 30–1000 $^\circ\text{C}$). Magnetic susceptibilities of metal complexes were determined using a Sheerwood Scientific MX Gouy magnetic susceptibility apparatus, and carried out using the Gouy method.

2.2. Synthesis

2.2.1. Ethyl 2-(2-phenyl-1H-benzo[d]imidazol-1-yl)acetate (**1**)

1.95 g 2-phenyl-1H-benzo[d]imidazole (10 mmol) was mixed with 2.80 g K_2CO_3 (20 mmol) in acetone and the solution was stirred for 2 h. 1.35 mL Ethyl bromoacetate (12 mmol) was added to the solution and stirred for 24 h at room temperature. This solution was added into water (200 mL) and the solid product filtered off. As a result of the reaction, esters (**1**) was crystallized from ethanol. $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$; M.W. = 280.12 g/mol; m.p. = 112–114 $^\circ\text{C}$; yield: 81%; IR $\nu(\text{C}=\text{O})$ 1742 cm^{-1} ; $(\text{C}-\text{O})$ 1215 cm^{-1} ; ^1H NMR (400 MHz, ppm, DMSO): δ = 1.15(t, 3H, O-CH $_2$ -CH $_3$), 4.11(d, 2H, O-CH $_2$ -CH $_3$), 5.61(s, 2H, N-CH $_2$ -CO), 7.27–8.62(m, 9H, Ar-H). Elemental Anal. Calc. $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.01; H, 5.64; N, 9.84%. MS(ESI): m/z : 280.98 (100.0%), 282.10 (18.0%) (**1.H $^+$).**

2.2.2. Ethyl 4-(2-phenyl-1H-benzo[d]imidazol-1-yl)butanoate (**2**)

1.95 g 2-phenyl-1H-benzo[d]imidazole (10 mmol) was mixed with 2.80 g K_2CO_3 (20 mmol) and stirred for 2 h in $(\text{CH}_3)_2\text{CO}$ (30 mL) at rt. After 2 h. 1.82 mL ethyl bromobutanoate (12 mmol, % 95) was added to the solution and stirred at rt for 24 h. This solution was added into water (200 mL) and the solid product filtered off. The crude product was crystallized from ethanol. $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$;

M.W. = 308.15 g/mol; m.p. = 107–109 $^\circ\text{C}$; yield: 90%; IR (ATR)/ cm^{-1} ($\text{C}=\text{O}$) 1724, $(\text{C}-\text{O})$ 1195; ^1H NMR (400 MHz, ppm, DMSO): δ = 1.08 (t, 3H, -O-CH $_2$ -CH $_3$); 1.94 (p, 2H), 2.25 (t, 2H, -N-CH $_2$ -CH $_2$ -CH $_2$ -CO-); 3.94 (q, 2H, -O-CH $_2$ -CH $_3$ -); 4.34 (t, 2H, -N-CH $_2$ -CH $_2$ -CH $_2$ -CO-); 7.2–8.3 (m, 9H, Ar-H); Elemental Anal. Calc. $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.81; H, 6.45; N, 9.24%; MS(ESI): m/z : 309.04 (100.0%), 310.02 (20.9%) (**2.H $^+$).**

2.2.3. 2-Phenylbenzimidazole-N-acetohydroxamic acid (N-hydroxy-2-(2-phenyl-1H-benzo[d]imidazol-1-yl)acetamide) (**HL** 1)

10.0 mmol of NaOMe (0.57 g) was added to 5.0 mmol of hydroxylamine hydrochloride (0.35 g) in 5 mL of absolute methanol and stirred for 10 min. The sodium chloride precipitate was filtered off. The prepared solution of free hydroxylamine was cooled in -5 $^\circ\text{C}$ and added on **1** (0.28 g, 1 mmol). The mixture was stirred at -5 $^\circ\text{C}$ until the compound reacted completely. The reaction mixture was acidified to pH 7 by a solution of HCl (10% v/v) to induce precipitation. The precipitate was filtered, washed with water and dried at 60 $^\circ\text{C}$. $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$; M.W. = 267.29 g/mol; m.p. = 198–200 $^\circ\text{C}$; yield: 71%; IR max ($\text{C}=\text{O}$) 1664 cm^{-1} , (N-H) 3239 cm^{-1} ; ^1H NMR (400 MHz, ppm, DMSO): δ = 4.98 (s, 2H, -N-CH $_2$ -CO); 7.45–8.00 (m, 9H, Ar-H); 9.36 and 9.68 (s, 1H, O-H); 10.68 and 11.22 (s, 1H, N-H); ^{13}C NMR (APT) (169.88, 164.27, 154.07, 143.90, 136.67, 130.42, 130.25, 129.75, 129.12, 122.97, 122.62, 119.57, 111.01, and 45.39 ppm); Elemental Anal. Calc. $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.64; H, 4.66; N, 15.52%; MS(ESI): m/z : 268.03 (100.0%), 269.08 (20.0%) (**HL** 1 .H $^+$).

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