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ORIGINAL PAPER

Spectral Characterization and Crystal Structures of Two Newly Synthesized Ligands of *N*-Methyl *O*-Substituted Benzohydroxamic Acids

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Abstract Two new derivatives of hydroxamic acid having the general formula *R*C(O)N(*R*N)OH (*R* = alkyl/aryl; *R*N = alkyl/aryl or H), have been synthesized by the condensation method in an ice-bath. The compounds, *N*-methyl *o*-iodobenzohydroxamic acid and *N*-methyl *o*-bromobenzohydroxamic acid have been isolated as crystalline solids, stable in air and soluble in organic solvents and in aqueous alcohol solution. A systematic investigation of the derivatives were carried out both in solid and in solution. They have been structurally characterized by elemental analysis, and the results were in good agreement with the values calculated for the proposed formula. These derivatives were further investigated on the basis of FT-IR, multinuclear ^{1}H, ^{13}C NMR spectroscopy, and Single Crystal X-ray crystallographic studies, indicating that both the compounds are structurally similar.

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Introduction

Hydroxamic acids [1] *R*C(O)N(*R*N)OH (*R* = alkyl/aryl; *R*N = alkyl/aryl or H), are among the some of the most well studied compounds due to the fact that they demonstrate a wide variety of biological activities and their significance in so many different applications in modern society. Much of their activity is due to their chelating properties with metal ions, hence constituting a very important class of chelating agents with versatile biological activities [2]. These compounds are capable of inhibiting a variety of enzymes, including ureases and matrix metalloproteinases [3–5]. Hydroxamic acid moieties are used as therapeutic targeting cancer, cardiovascular diseases, HIV, Alzheimer's, malaria, allergic diseases and metal poisoning [6–12]. Moreover, the hydroxamic acids have been used as insecticides [13] and antimicrobials [14]. They are also employed industrially as antioxidants [15], as inhibitors of corrosion [16], and for the extraction of toxic elements [17]. A number of synthetic routes are available for the preparation of hydroxamic acids and have been well-documented in the literature [18], but some of them are tedious, time consuming and also expensive. The reasonable way of producing hydroxamic acid derivative is the reaction of hydroxylamine with acid chlorides or esters [19]. Hydroxamic acids are weak acids with p*K*a values of the N–OH proton in aqueous solvents of the order 8.5–9.4 [20]. Furthermore, studies have shown that in non-protic solvents, such as dimethylsulfoxide (DMSO), some hydroxamic acids, including benzohydroxamic acid (**1a**: R_C = Ph, *R*N = H) act as N–H acids, rather than as N–OH

acids [21, 22]. Primary hydroxamic acids (**1**) (R_1 = H) can go through two consecutive deprotonating proceedings, loss of the first proton yields the hydroxamate anion (**2**), and loss of the second proton yields the hydroximate di-anion (**3**). The hydroxamic acid, hydroxamate and hydroximate groups can exhibit *cis*/*trans* or (*Z*, *E*) isomerism (**1a, 1b**) resulting from the free rotation about the C–N bond, keto (R_CC(O)N(OH)R_1)-enolic (R_CC(OH)N(OH)) tautomerism (**1b, 1c**), as shown (Fig. 1), and have several resonating structures [23–25].

Keeping in view the structural and biological diversity of hydroxamic acids, herein we report two new hydroxamic acids.

Experimental

Materials and Methods

The chemicals were purchased from Aldrich and were used as received. All the chemicals were of analytical grade. The percentage compositions of the elements (CHN) for the compounds were determined using an elemental analyzer CHNS-O Model Fison EA 1108. Solid state infrared spectra of the compounds are recorded in the range 4,000–400 cm^{-1}. The infrared spectra were recorded as potassium bromide discs using a Perkin-Elmer spectrophotometer GX. The ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded using the BRUKER FT-NMR 600 MHz Cryo-Prob spectrometer, using d6-DMSO as a solvent and tetramethylsilane as an internal standard. Crystals structures determination were carried out on a Bruker Smart APEX CCD area detector diffractometer equipped with graphite mono-chromatised Mo-K_α (λ = 0.71073 Å) radiation in each case. All data collection was carried out at 100 K. The program *APEX2* [26] was used for collecting frames of data, indexing of reflections and determination of lattice parameters, *SAINT* [26] for absorption correction, and SHELX97 [27].

Synthesis of Ligand (1)

The titled compound *N*-methyl *o*-iodobenzohydroxamic acid ($C_8H_8INO_2$) was prepared by the dropwise addition of *o*-iodobenzoyl chloride (2.66 g, 0.01 mol) to a stirred cold solution of *N*-methylhydroxylamine (0.84 g, 0.01 mol) containing sodium hydrogen carbonate (1.80 g, 0.02 mol), for 30 min at 4 °C. The solution was filtered and reduced to evaporate at low pressure which afforded a precipitate. The precipitate was then dissolved in boiling ethyl acetate to remove any undissolved substance and then the filtrate is

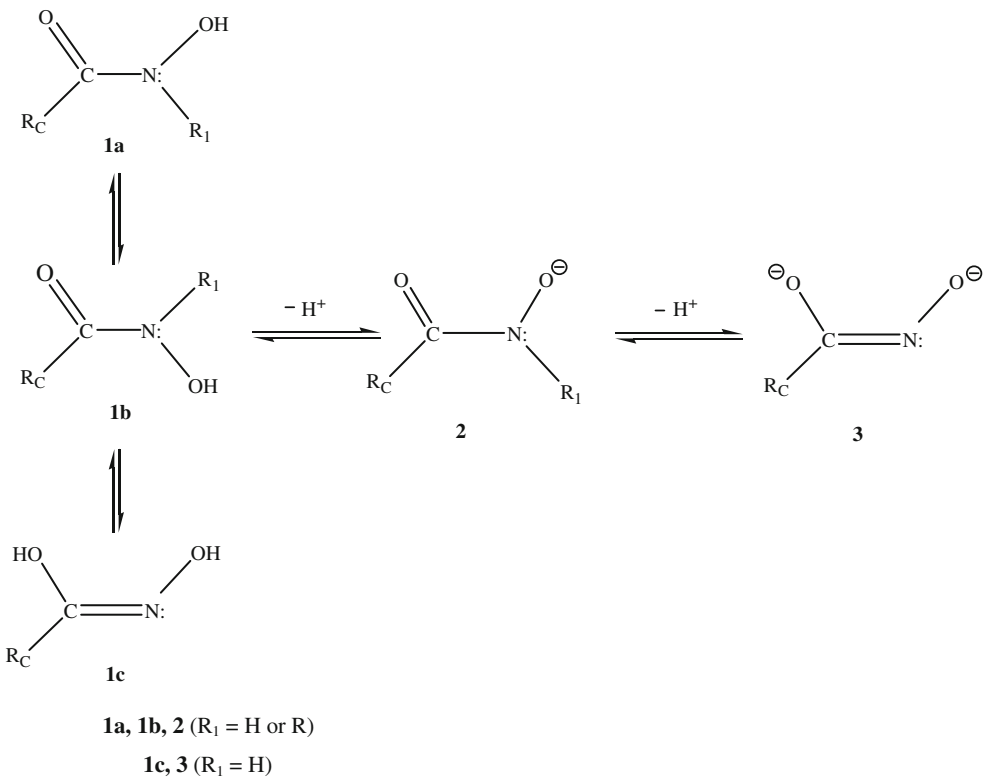

Fig. 1 Structures of hydroxamic acids (**1**), hydroxamates (**2**) and hydroximates (**3**), E↔Z isomerism (**1a, 1b**), keto↔enol tautomerism (**1b, 1c**)

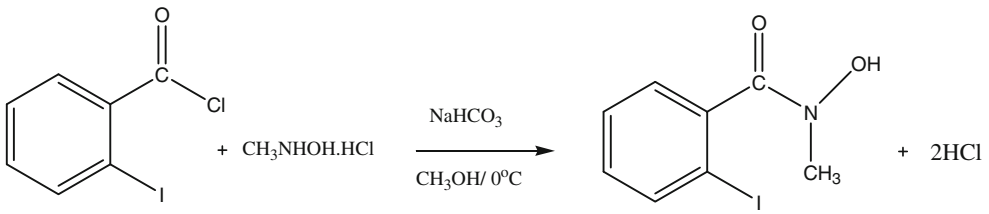

Fig. 2 Conversion of *o*-iodobenzoyl chloride to *N*-methyl *o*-iodobenzohydroxamic acid (1)

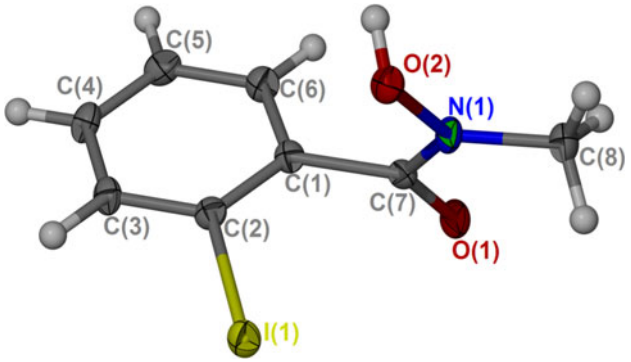

Fig. 3 Thermal ellipsoidal plot of C_8 H_8 I N O_2. Displacement ellipsoids are drawn at the 50 % probability level, and H atoms are shown as spheres of arbitrary radii

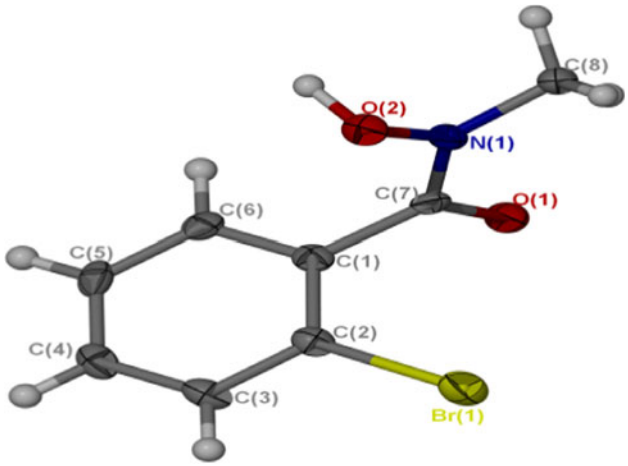

Fig. 4 Thermal ellipsoidal plot of C_8 H_8 Br N O_2. Displacement ellipsoids are drawn at the 50 % probability level, and H atoms are shown as spheres of arbitrary radii

placed at 4 °C overnight to afford single crystals (Fig. 2). Yield: 84 %. Melting point: 134–135. Analysis: Calcd. (%): C 34.67, H 2.89, N 5.06. Found (%): C 35.32, H 2.71, 4.93. Selected IR data (KBr pellets): 3,114(b, ν O–H), 1,608 (s, ν C = O), 1,494 (s, ν C–N) and 915(s, ν NO).

Synthesis of Ligand (2)

The titled compound *N*-methyl *o*-bromobenzohydroxamic acid ($C_8H_8BrNO_2$) was prepared in a similar method as for (1), by using *o*-bromobenzoyl chloride (2.19 g, 0.01 mol).Yield: 87 %. Melting point: 127–128 Analysis: Calcd. (%): C 41.76, H 3.48, N 6.10. Found (%): C 39.60, H 2.98, 6.01. Selected IR data (KBr cm^{-1}): 3,123(b, *v* O–H), 1,600 (s, *v* C = O). 1,436 (s, *v* C–N) and 915(s, *v* NO).

X-ray Crystallography

The single crystals of *N*-methyl *o*-iodobenzohydroxamic acid and *N*-methyl *o*-bromobenzohydroxamic acid (Figs. 3 and 4) of suitable quality were each mounted on a fine glass capillary and aligned on the Bruker SMART APEX2 diffractometer, equipped with graphite mono-chromated Mo-K_α radiation source (λ = 0.71073 Å). The range for data collection was 2.67–25.50 for (1) and 2.78–25.98 for (2). All calculations were performed using the SHELXTL-97 package [28]. The data collection and refinement parameters are summarized in Table 1. Selected bond lengths and angles are given in Tables 2 and 3.

Crystallographic data for the compounds (1) and (2) have been deposited with the Cambridge Crystallographic Data Centre, CCDC reference numbers (920,545 and 920,539). This information may be obtained free of charge from: the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail:deposit@ccdc.cam.ac.uk; website: http://www.ccdc.cam.ac.uk).

Results and Discussion

The characteristic infrared frequencies for both compounds have been observed in their specific range. The ν(OH) band is located within the range 3,123–3,114 cm^{-1} as broad bands. The carbonyl, ν(CO) stretching vibrations positioned within the range 1,608–1,600 cm^{-1} significantly, below the typical ketonic ν(CO) of 1,715–1,680 cm^{-1} [29–37], reflecting the fact that the vibration is at an appreciably lower frequency than the carbonyl absorption of normal ketones, which may be caused by the resonance effect of the ionic form. Moreover the significant shift of ν(C = O) to lower frequency together with the broad ν(O–H) band is

Table 1 Crystal data and structure refinement for the ligands 1 and 2

Compound	(1)	(2)
Gross formula	C_8 H_8 I N O_2	C_8 H_8 Br N O_2
M	277.05	230.06
Crystal system, space group	Orthorhombic, Pbca	Orthorhombic, Pbca
Crystal shape	Block	Block
Color	Colorless	Colorless
a, Å	8.3319(14)	9.0280(17)
b, Å	13.945(2)	13.063(3)
c, Å	15.245(3)	14.634(3)
α, deg	90.00	90.00
β, deg	90.00	90.00
γ, deg	90.00	90.00
V, Å^3	1,771.3(5)	1,725.8(6)
Z	8	8
d_c (Mg/m^3)	2.078	1.771
F(000)	1,056	912
μ(mm^{-1})	3.573	4.720
T, K	100(2)	100(2)
Crystal size, mm	0.40, 0.25, 0.10	0.20, 0.15, 0.07
Measured reflections	21,271	19,981
Independent reflections	2,174	1,981
Reflections with I > 2 (I)	1,600	1,493
R_{int}	0.0632	0.0691
θ_{max}	28.19°	27.50°
θ_{min}	2.67°	2.78°
Completeness to theta	0.999	1.00
h	−11 11	−11 11
k	−18 18	−16 16
l	−20 20	−19 19
$R[F^2 > 2\ (F^2)]$	0.0291	0.0313
$wR(F^2)$	0.0597	0.0557
S	1.029	1.058
Reflections	2,174	1,981
Parameters	111	111
Restraints	0	0
$_{max}$e Å^{-3}	1.068	0.776
$_{min}$e Å^{-3}	−0.875	−0.699

$w = 1/[\sigma^2(F_o^2) + (0.0266P)^2 + 3.9774P]$ where $P = (F_o^2 + 2F_c^2)/3$

$w = 1/[\sigma^2(F_o^2) + (0.1053P)^2 + 7.2069P]$ where $P = (F_o^2 + 2F_c^2)/3$

related with intramolecular hydrogen bonding for primary hydroxamic acids [38] and intermolecular hydrogen bonding for hydrated compounds [39]. In general, the ν(C–N) and ν(N–O) bands occur as a sharp peak in the ranges 1,494–1,436 and 915 cm^{-1}, respectively [40]. The free hydroxamic acids have been shown to exist principally in the keto form in solid state or in polar solvents [41, 42]. The ^{1}H and ^{13}C NMR spectra at room temperature have been proven valuable in establishing the nature and

Table 2 Selected bond lengths (Å) for the ligands 1 and 2

(1)		(2)	
I1 C2 2.103(4)	C1 C6 1.394(5)	Br1 C2 1.897(3)	C1 C6 1.390(4)
N1 C7 1.320(5)	C1 C7 1.499(5)	O1 C7 1.239(3)	C1 C7 1.502(4)
N1 O2 1.396(4)	C2 C3 1.391(5)	O2 N1 1.390(3)	C2 C3 1.381(4)
N1 C8 1.458(5)	C3 C4 1.384(6)	N1 C7 1.331(3)	C3 C4 1.383(4)
O1 C7 1.249(5)	C4 C5 1.383(6)	N1 C8 1.444(3)	C4 C5 1.376(4)
C1 C2 1.391(5)	C5 C6 1.390(6)	C1 C2 1.383(4)	C5 C6 1.388(4)

structure of the ligands, which were further supported by X-ray diffraction studies. The ^{1}H NMR spectrum of compound 1 and 2 show broad signals at lower field 10.28 and 10.39 ppm, which are assigned to the OH protons thus indicating the formation of the ketonic form even in solution. The aromatic protons appear as signals at 7.09–7.86 ppm and 7.22–7.64 ppm with an integration equal to four protons corresponding to the protons attached to the carbons. The methyl protons appeared as singlets at 3.244, in both compounds. The ^{13}C NMR spectra for compound 1 and 2 show downfield peaks at 169.02 ppm and 168.28 were due to the carbonyl group C (7). The aryl carbon C (1) attached to the carbonyl group appeared downfield at 165.92 and 164.46 ppm. The aryl carbon C (2) attached to the iodo and bromo group appeared upfield at 93.39 and 118.80 ppm respectively. The signals at 127.68–142.56 ppm and 127.88–138.18 ppm are assigned to the aromatic carbons. The signals which appeared at 38.88 and 38.59 ppm are likely to arise from methyl C (8) attached to the nitrogen atom.

Crystal Structure Analysis

The crystal structures of the ligand *N*-methyl *o*-iodobenzohydroxamic acid (1) and *N*-methyl *o*-bromobenzohydroxamic acid (2) are depicted in Figs. 3 and 4 are basically similar structures. The carbonyl oxygen and the hydroxyl oxygen in both halogen substituted benzohydroxamic acid are *trans* to each other, probably due to the steric influence between the methyl substituent on the hydroxamate fragment with the halogen atom in both compounds. As a result, there is absence of any intramolecular hydrogen bonding between the hydroxyl group and the carbonyl oxygen in the two structures. However, strong intermolecular hydrogen bonds are found between the hydroxyl group and the carbonyl oxygen atoms of adjacent molecules. (Fig. 5), (1): O1···O2 2.598(4) Å, symmetry operator x − 0.5, 0.5 − y, 1 − z; (Fig. 6), (2): O1···O2 2.641(3), symmetry operator x − 0.5, 0.5 − y, −z). The plane occupied by the methyl substituted hydroxamic acid fragment (excluding the hydrogen atoms) is evidently flat in both compounds (1) and (2), with RMS deviation from planarity of 0.0106 and 0.0336 Å, respectively. These

Table 3 Selected bond angles (deg) for the ligands 1 and 2

(1)		(2)	
C7 N1 O2 120.1(3)	C3 C2 I1 117.6(3)	C7 N1 O2 118.8(2)	C1 C2 Br1 119.9(2)
C7 N1 C8 123.2(3)	O1 C7 N1 119.9(4)	C7 N1 C8 125.6(2)	O1 C7 N1 121.4(3)
O2 N1 C8 116.6(3)	O1 C7 C1 121.1(4)	O2 N1 C8 114.8(2)	O1 C7 C1 121.9(2)
C1 C2 I1 120.9(3)	N1 C7 C1 118.9(3)	C3 C2 Br1 118.4(2)	N1 C7 C1 116.7(2)

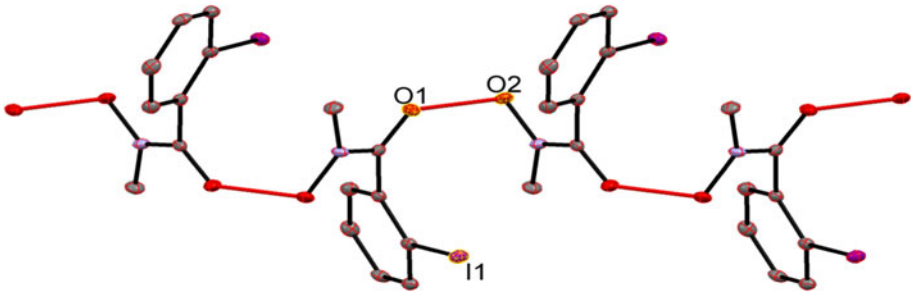

Fig. 5 Polymeric chains of (1), depicting the presence of hydrogen bonding interaction between the hydroxyl group with the carbonyl oxygen of adjacent molecules, symmetry operator: −0.5 + x, 0.5 − y, 1 − z

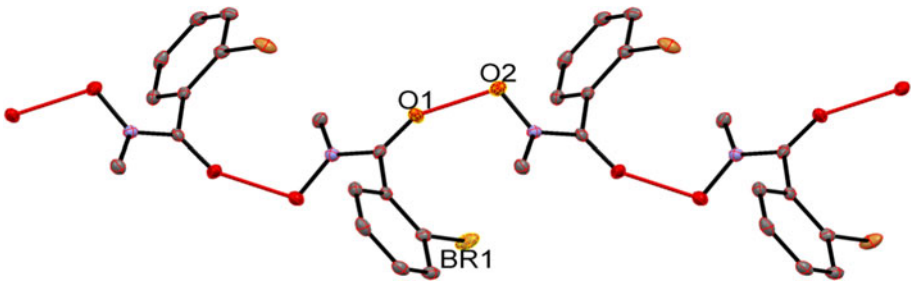

Fig. 6 Polymeric chains of (2), depicting the presence of hydrogen bonding interaction between the hydroxyl group with the carbonyl oxygen of adjacent molecules, symmetry operator: −0.5 + x, 0.5 − y, − z

planes make an angle of 72.7(1)° and 85.3(1)° with the phenyl rings in ligands (1) and (2), respectively.

Conclusion

Both the ligands were prepared successfully and gave sharp melting points, indicating that the compounds are pure. The single crystal X-ray diffraction studies supported the spectral characterization and further illustrated that both the compounds are basically having the same structure.

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