Journal of Molecular Structure 1130 (2017) 46–54

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Synthesis, structural and spectroscopic studies of two new benzimidazole derivatives: A comparative study

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ARTICLE INFO

Article history:
Received 8 June 2016
Received in revised form
28 September 2016
Accepted 4 October 2016
Available online 5 October 2016

Keywords:
Characterization
Benzimidazole
FT-IR
^{1}H and ^{13}C NMR
DFT calculations

ABSTRACT

In the present work, structural and spectroscopic studies on 1-Methyl-2-(2′-hydroxy-4′-chlorophenyl) benzimidazole **(1)** and 1-Methyl-2-(2′-hydroxy-4′-methoxyphenyl)benzimidazole (**2**), have been carried out extensively by X-ray diffraction, HRMS, UV–Vis, FT-IR and ^{1}H and ^{13}C NMR spectroscopy. The crystal structure of both compounds is stabilized by O–H···N hydrogen bond and π-π interactions. Contrary to compound **1**, the skeleton of compound **2** is considerably deviated from the planarity probably caused by intermolecular hydrogen bonding. The experimental results were compared to the theoretical ones, obtained at DFT level. Ground state geometry, electronic structure, vibrational and NMR spectra have been performed using the B3LYP functional with the 6-31 G(d,p) basis set. It was observed that the bond distances and angles in the both compounds were in good with those of the experiment. The energetic behaviors of the both compounds in methanol solvent were examined using by time-dependent DFT (TD-DFT) method by applying the polarizable continuum model (PCM). Isotropic chemical shifts (^{13}C and ^{1}H NMR) were calculated using the gauge-invariant atomic orbital (GIAO) method. The HOMO and LUMO analyses were used to elucidate information regarding charge transfer within the molecule.

1. Introduction

The benzimidazole nucleus is one of the most significant N-containing fused organic compounds in a large diversity of natural products and synthetic pharmaceutical materials [1–4]. The benzimidazole derivatives are known to demonstrate various biological properties [5–8]. Several drugs have been developed based on benzimidazole nucleus and marketed by various pharmaceutical companies [9–11]. Moreover, benzimidazole scaffolds have also been found important in other suitable fields such as material science [12–17], agrochemicals [18], and explosives [19]. A diversity of conventional procedures has been informed for the preparation of benzimidazoles [20–29]. One of the popular conventional methods for the preparation of these important compounds is cylization of *o*-phenylenediamine with carboxylic acids or aldehydes.

Diversified and highly substituted benzimidazole molecules have tremendous importance in drug discovery owing to their unique and selective binding abilities for the biological targets with respect to their chemical functionalization [30]. Taking these above facts into account, the goal of this study is to perform an experimental and computational work on benzimidazole including a hydroxyl group using the quantum chemical theories so as to help to make further examine on the spectroscopic and structural properties. Firstly, we have synthesized and characterized **1** and **2** (Scheme 1) using UV–Vis, ^{1}H/^{13}C NMR, FT-IR, and X-ray diffraction spectroscopic techniques.

2. Materials and methods

5-Chlorosalicylaldehyde, 5-Methoxysalicylaldehyde and *N*-methyl-1,2-phenylenediamine were purchased from the Merck, Fluka and Aldrich, respectively. All other reagents and solvents were reagent grade quality and were obtained from commercial suppliers.

2.1. Analytical instruments and spectroscopy techniques

Follow-up of the reactions and checking the purity of the

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http://dx.doi.org/10.1016/j.molstruc.2016.10.013
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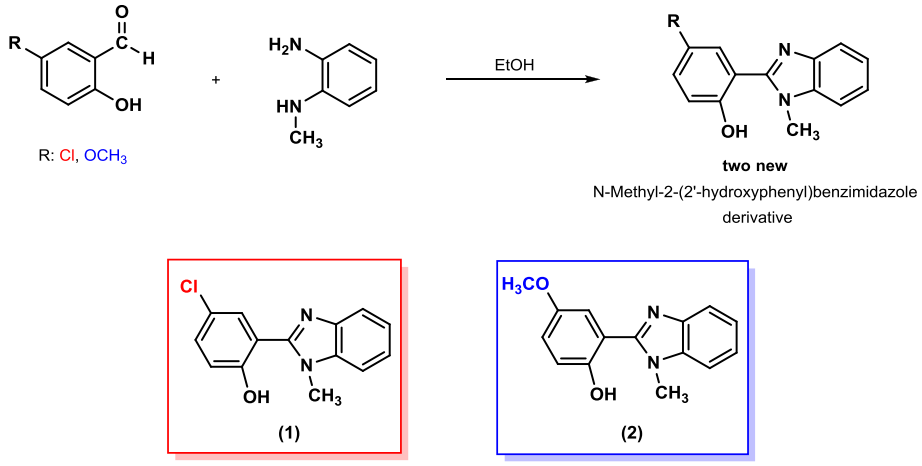

Scheme 1. Structures of synthesized benzimidazole.

compounds were carried out on the silica gel GF-254 under UV at 254 nm. The melting points were checked by using Stuart SMP30 apparatus. The room temperature fourier transform infrared spectra of the compounds were measured on a Vertex 80V Bruker FT-IR spectrophotometer in the 4000–400 cm^{-1} region with 4 cm^{-1} resolution using KBr pellets. UV–Vis spectra were carried out by using a Unicam spectrometer in the wavelength range 900–200 nm. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AVANCE III 400 MHz spectrometer. Internal lock was provided by a deuterated DMSO solvent (δ = 39.51 ppm) and both proton and carbon signals were referenced to TMS. All NMR spectra were measured at room temperature. High resolution mass spectra were recorded on a SHIMADZU QP2010S GC-MS. The thermal gravimetric analysis was carried out using a SHIMADZU DTG-60H.

2.2. Synthesis

2.2.1. Typical procedure for the synthesis of benzimidazoles

A mixture of substituted salicylaldehyde (0.12 g, 0.98 mmol) and *N*-methyl-1,2-phenylenediamine (0.12 g, 0.98 mmol) in absolute ethanol (20 ml) was stirred. The mixture was refluxed for 3 h. The reaction was monitored by checking TLC. After completion of the reaction, solvent was removed under reduced pressure from the reaction mixture. Then solid product was purified by recrystallization from ethyl acetate (EtOAc) without using any column chromatography to give pure product [31]. The prepared compounds were identified by their melting point determination and further characterized by FT-IR and NMR (400 MHz Bruker) studies.

*2.2.1.1. 1-Methyl-2-(2′-hydroxy-4′-chlorophenyl)benzimidazole (**1**).* Colour light-brown crystals (0.19 g, yield 74%); m.p. 136–139 °C. EIMS: *m/z* 258 [M+], 257, 241, 223, 97, 77.^{1}H NMR: δ: 3.79 (s, 3H; H_1), 7.07–7.09 (d, 1H; H_5, J:8.0 Hz), 7.24–7.33 (m, 2H; H_7, H_8), 7.43–7.45 (d,d 1H; H9, J:2.8, 2.8 Hz),7.59–7.60 (d, 1H; H2, J:2.8 Hz), 7.61–7.63 (d, 1H; H6, J:8.0 Hz),7.68–7.70 (d, 1H; H4, J:8.0 Hz), 11.28 (s, 1H; H10) ppm; ^{13}C NMR: δ: 31.8 (C7), 110.9 (C5), 118.5 (C4), 118.5 (C2), 119.1 (C3), 122.5 (C14), 123.0 (C12), 123.1 (C11), 130.4 (C9), 131.5 (C6), 136.2 (C1), 142.1 (C13), 150.9 (C8), 155.8 (C10) ppm.

*2.2.1.2. 1-Methyl-2-(2′-hydroxy-4′-methoxyphenyl)benzimidazole (**2**).* Colour light-brown crystals (0.19 g, yield 74%); m.p. 139–142 °C. EIMS: *m/z* 254 [M+], 239, 237, 211, 183, 77.^{1}H NMR: δ: 3.76 (s, 3H; H1), 3.82 (s, 3H; H11), 6.97–7.03 (m, 1H; H5, H9), 7.15 (s, 1H; H2), 7.24–7.33 (m, 2H; H7, H8), 7.60–7.62 (d, 1H; H4, J:8.0 Hz), 7.68–7.70 (d, 1H; H6, J:8.0 Hz), 10.54 (s, 1H; H10) ppm. ^{13}C NMR: δ: 31.9 (C7), 56.2 (C15), 110.8 (C5), 115.3 (C2), 116.7 (C4), 117.7 (C3), 118.1 (C12), 119.0 (C14), 122.4 (C11), 122.8 (C9), 136.2 (C6), 142.1 (C1), 150.7 (C8), 152.2 (C13), 152.3 (C10) ppm.

2.3. X-ray diffraction analysis

The crystallographic data were collected on an Agilent Technologies SuperNova [32], (single source at offset and Eos CCD detector) diffractometer with SuperNova (Mo) X-ray Source (Mo Ka, k = 0.71073 Å) at 293 K (Table 1). A CrysAlisPro [32] program package was used for the determination of cell parameters, data integration and absorption correction. All the calculations were carried out using the program SHELXS-97 [33] and SHELXL-97 [33]. All carbon hydrogens were positioned geometrically and refined using a riding model. The remaining hydrogen atoms were located from the Fourier Difference map. Molecular figures were obtained using DIAMOND 3.0 (demonstrated version) [34].

2.4. DFT calculations

All calculations were performed using the GAUSSIAN program [35] (version 03). The crystal structure was used as an initial molecular geometry. The output files were visualized via GAUSSIAN VIEW 03 software [36]. The molecular structures of both compounds in the ground state were optimized using DFT with hybrid functional B3LYP (Becke's three parameter hybrid functional using the LYP correlation functional) at 6-31G (d,p) basis set [37,38]. On the basis of the optimized ground state geometry, the absorption spectral properties were calculated by TD-DFT approach associated with the polarizable continuum model (PCM) [39]. The vibrational harmonic frequencies of the compounds were calculated using the DFT/B3LYP hybrid functional with 6-31G (d,p) basis set. None of the predicted vibrational spectra having any imaginary frequency prove that optimized geometry is located at the lowest point on the potential energy surface. Considering the solvent effect of DMSO solution the ^{1}H and ^{13}C NMR chemical shifts were calculated for the DMSO solvent using the GIAO method [40–42].

3. Results and discussion

3.1. Molecular structure of compounds **1** and **2**

The crystal structures of two 1-methyl-imidazole derivatives are presented in Figs. 1–2 and their crystallographic data are summarized in Table 1. Crystal packing diagrams of both compounds are