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Synthesis and conformational study of a new class of highly bioactive compounds

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Abstract

Several conformers of the bioactive Morita–Baylis–Hillman adducts (MBHA) **1**–**4** were studied. Relaxed potential energy surfaces scan (RPESS) have been performed. The principal structures obtained from RPESS approach were then fully optimized at B3LYP/6-311++G** level and with PCM model simulating water media at B3LYP/6-31+G* level. The relative stabilities obtained for conformers **1**, **2** and **4** in gas and water media are different. Six and seven member intramolecular hydrogen bonds (IHBs) have been characterized for adducts **1** and **4**, respectively, through atoms in molecules (AIM) calculations. The occurrence of such type of IHBs was also supported by IR and ^{1}H NMR spectroscopic data.

1. Introduction

Morita–Baylis–Hillman reaction [1] yields adducts such as **1** from simple starting compounds, in a single-pot reaction. All atoms from the substrate are present in the product and the reaction can be carried out in water or other non-toxic solvents, being a classic example of a green chemistry reaction [2]. Due to the synthetic utility of such products, several protocols have been achieved to improve the yields of this reaction [3].

The bioactivity of the Morita–Baylis–Hillman adducts-(MBHA) were first described by Kundu [4]. In our continuing search for bioactive substances [5–7], we recently have discovered that **2** and **3** (Fig. 1) are very efficient Leishmanicidal (from *in vitro* activities against *Leishmania amazonensis* [6]). Curiously, the similar compound **1** is not as active as **2**. Topological differences in the series **1**–**4** can be determining for their different Leishmanicidal activities [6]. Our group described that **1**, **2**, **3** and several other aromatic MBHA are very toxic against the aquatic gastropod mollusk *Biomphalaria glabrata* (Say), the main intermediate host of schistosomiasis [7]. We have also verified that the compound **4** is not as toxic as its isomer **3**, for *Artemia salina* Leach [8]. Thereafter Almeida et al. reported a high antiproliferative effect for **1** and **3** on human tumor cell lines [9].

In one of the approaches to verify the occurrence of a hydrogen bond (HB), especially in crystallography, the HB distance is compared with the sum of the atomic van der Waals (vdW) radii. In the OH···OC case, and using the values suggested by Pauling [10], a HB takes place if the distance between the proton donor–acceptor species is shorter than the sum of the vdW radii, 2.6 Å. An alternative approach results from AIM theory [11], from which a bond between atoms can be assigned from bond critical points (BCP). Such methodology have been successfully applied in the study of several hydrogen-bonded systems [12,13].

The purpose of this Letter is to present a conformational study at DFT level in gas phase and DFT/PCM (water) level of a new class of drugs (**1**–**4**) and a new synthetic protocol to prepare **3** and **4**. Besides, the occurrence of

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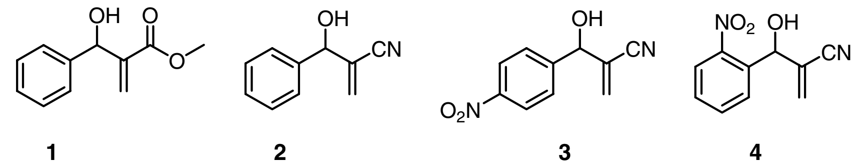


Fig. 1. The Morita–Baylis–Hillman adducts studied in this Letter.

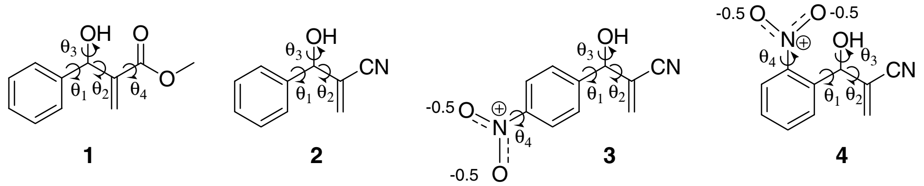


Fig. 2. The dihedral angles investigated for molecules **1**–**4**.

IHBs in these molecules is also characterized through AIM methodology, IR and ^{1}H NMR spectroscopic data.

2. Computational procedure

For each dihedral angle shown in Fig. 2 relaxed potential energy surface scan (RPESS) calculations have been performed, for **1**–**4** MBHA, using B3LYP functional [14,15] with the 6-31+G* basis-set. These dihedral angles varied from 0° to 360°, in steps of 30°. The obtained minima thus were then fully optimized, without any symmetry constraint, at B3LYP/6-311++G** level in gas phase and B3LYP/6-31+G* in water using polarized continuum model (PCM) [16] in order to simulate the solvent. All calculations were carried out using GAUSSIAN 98W [17] in a Pentium 4-HT (3.2 GHz) with 3Gb/RAM. The nature of the electronic density on IHB on **1** and OH···O←N=O on **4** have been investigated through Bader's AIM theory using the AIM 2000 1.0 package [18].

3. Experimental section

3.1. Synthesis of 3–4

MBHA were carried out using the corresponding aldehydes (1 mmol), 0.4 mL of acrylonitrile as the activated alkene and 1 mmol of DABCO as promoter at 0 °C for 15 and 40 min, respectively, for **3** and **4**. The reaction media was filtered on silica gel, using AcOEt–hexane (2:8) as solvent and the crude reaction product concentrated under reduced pressure (both yields of isolated **3** and **4** were >99%). In this work the AMBH **1** and **2** were not prepared. These spectroscopic data can be seen in the literature [19,20].

3.2. 3-Hydroxy-2-methylene-3-(4-nitrophenyl) propanenitrile (3)

IR (KBr): 3447 (*fine band*), 3115, 2228, 1599, 1520, 1348, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.21 (d, $J = 8.8$ Hz, 2H); 7.58 (d, $J = 9$ Hz, 2H); 6.07 (d, $J = 0.8$ Hz, 1H); 6.16 (d, $J = 0.6$ Hz); 5.32 (s, 1H, *carbinolic hydrogen*); 3.23 (sl, 1H, *OH*).

3.3. 3-Hydroxy-2-methylene-3-(2-nitrophenyl) propanenitrile (4)

IR (KBr): 3345 (*large band*), 2228, 1348, 1609, 1520 cm^{-1}; NMR ^{1}H ($CDCl_3$, 200 MHz) δ ppm: 8.01 (dd, $J_1 = 8.0/J_2 = 1.4$ Hz, 1H); 7.84 (dd, $J_1 = 6$ Hz, $J_2 = 1.8$ Hz, 1H); 7.72 (ddd, $J_1 = 8.0$ Hz, $J_2 = 1.8$ Hz, $J_3 = 1.4$ Hz, 1H); 7.52 (ddd, $J_1 = 8.0$ Hz, $J_2 = 1.6$ Hz, $J_3 = 1.4$ Hz, 1H); 6.12 (d, $J_1 = 1.4$ Hz, 1H); 6.09 (d, $J_1 = 1.2$ Hz, 1H); 6.02 (s, 1H, *carbinolic hydrogen*).

Table 1

Thermochemical parameters calculated at B3LYP/6-311++G** level (at 298.15 K and 1 atm in gas phase) and electronic energies, ε_0, were obtained from PCM solvent model at B3LYP/6-31+G* level[a,b]

Conf.	Gas phase			Water
	ε_0 + ZPE (a.u.)	$\varepsilon_0 + G_{corr}$ (a.u.)	ΔG (kcal mol^{-1})	ε_0 (a.u.)
1a	−652.028774	−652.069861	–	−652.089199
1b	−652.028083	−652.069241	0.39	−652.089580
1c	−652.026615	−652.067770	1.31	−652.088251
1d	−652.022785	−652.061990	5.44	−652.091558
2a	−516.390613	−516.428240	1.69	−516.453454
2b	−516.390313	−516.428128	1.76	−516.468968
2c	−516.390333	−516.427930	1.88	−516.452848
2d	−516.392867	−516.430929	–	−516.453622
2e	−516.390472	−516.428299	1.65	−516.453948
3a	−720.949861	−720.991955	1.38	–
3b	−720.950099	−720.992255	1.19	–
3c	−720.949556	−720.991660	1.56	–
3d	−720.951909	720.994147	–	–
3e	−720.950782	720.993118	0.65	–
4a	−720.943762	−720.984396	1.69	−720.957763
4b	−720.946647	−720.987092	–	−720.975201
4c	−720.945567	−720.986741	0.22	−720.961445

[a] **1a**, **2d**, **3d** and **4b** are the reference minima for each compound.

[b] **1d**, **2b** and **4b** are the minima for each compound obtained using PCM calculations.

4. Results and discussions

First, in Table 1 we present the more stable conformations obtained for **1**–**4** in gas phase and the following thermochemical properties (298.15 K, 1 atm): sum of electronic and zero-point energies ($\varepsilon_0 + \mathrm{ZPE}$), sum of electronic and thermal free energies ($\varepsilon_0 + G_{\mathrm{corr}}$) and ΔG, obtained from the difference between $\varepsilon_0 + G_{\mathrm{corr}}$ for each conformation and the corresponding value for the more stable minimum. The corresponding structures can be visualized in Fig. 3. We also reported in Table 1 calculated electronic energies for **1**, **2** and **4** conformers obtained in water media.

We can see in Fig. 3 all the selected minima for the compound **1** (**1a**, **1b** and **1c**). The **1a** conformer corresponds to the lowest energy minimum for **1**. In **1a** and **1b** there is a clear evidence of IHB (C=O···HO), that can be important for the stability of these molecules in gas phase. In **1c** there is an evidence of IHB between $CH_3O\cdots HO$, which is weaker than the C=O···HO. The conformation **1d** is not a minimum in gas phase, but it has the lowest electronic energy in water.

All the selected minima for **2** and **3** do not show any CN···HO IHBs. In the most stable conformers **2d** and **3d** in gas, the hydroxyl and nitrile groups are preferentially in an antiperiplanar relative position (Fig. 3). Differently, the gauche conformation **2b** is the most stable in water.

Five important conformational minima were observed for **3** in gas phase. The geometry of the most stable conformer **3d** is very similar to the geometry obtained for its analogous **2d**, except for the existence of a nitro group in a *para* position. However, when there is a NO_2 group in *ortho* position (molecule **4**), both of the conformational

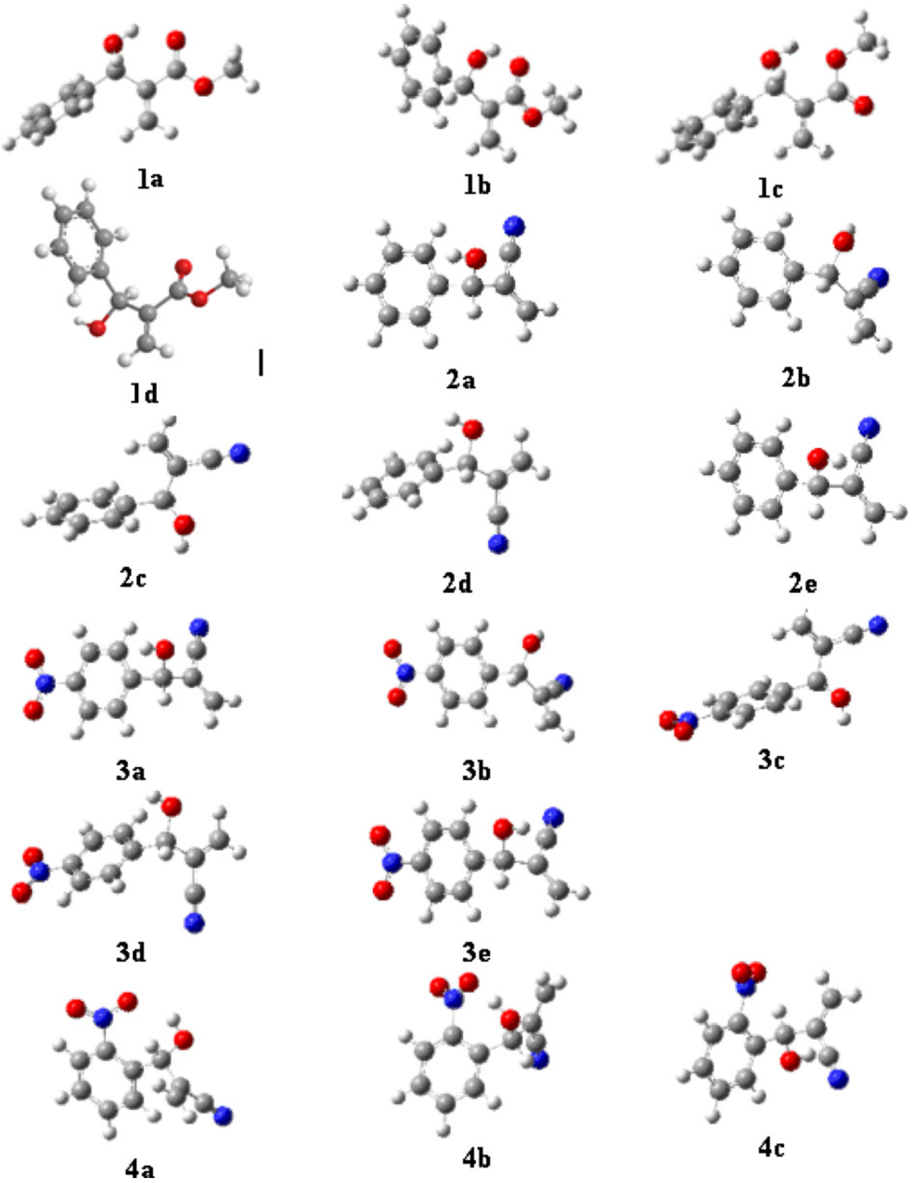

1a **1b** **1c**
1d **2a** **2b**
2c **2d** **2e**
3a **3b** **3c**
3d **3e**
4a **4b** **4c**

Fig. 3. Conformational structures obtained for adducts **1**–**4**. IHB distances (in Å) in gas phase for **1a**, **1b**, **1c** and **4b**, respectively, 2.078, 2.044, 2.109, 1.896.

energy minima (gas and water) corresponding to **4b** shows an IHB seven member ring ($\mathrm{OH}\cdots\mathrm{O} \leftarrow \mathrm{N{=}O}$), with the intramolecular distance of 1.896 Å and 1.973 Å, respectively.

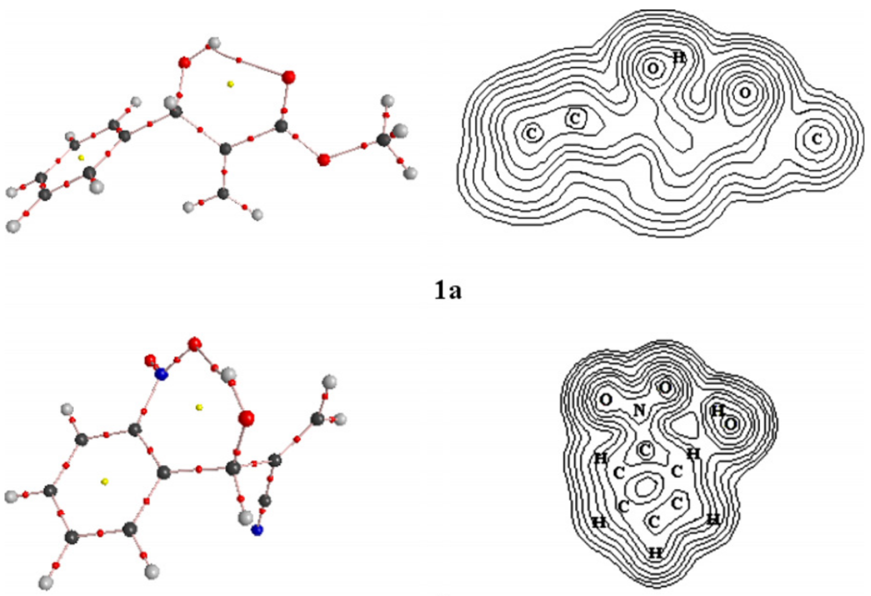
The AIM calculations, which were performed in order to confirm our IHBs hypothesis, demonstrated the presence of a bond critical point (BCP) between the proton donor and acceptor groups. We present, in Table 2, the characteristics of electronic density ρ and the laplacian of electronic density $\nabla^2\rho(r)$ (see Eq. (1)) at BCP, indicating the presence of two types of IHBs: (i) a six member ring on **1a** and (ii) a seven member ring on **4b** (Table 2, Fig. 4).

Table 2
Topological parameters obtained from AIM calculations

MBHA	1a		4b	
	ρ_{BCP}	∇^2_{BCP}	ρ_{BCP}	∇^2_{BCP}
$\mathrm{OH}\cdots\mathrm{OC}$	0.01840	−0.01704	0.02758	−0.02458

$$\left(\frac{\hbar^2}{4m}\right)\nabla^2\rho(r) = 2G(r) + V(r) \tag{1}$$

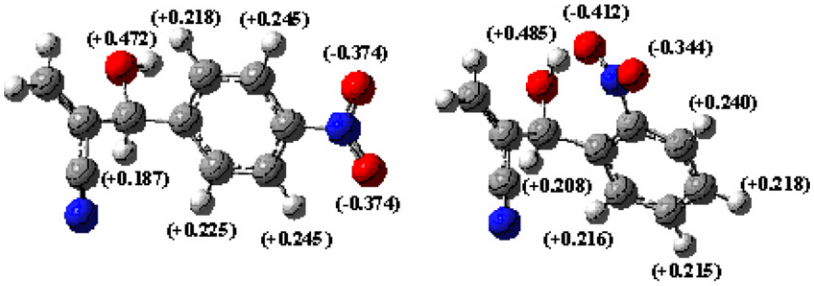
Eq. (1) corresponds to the Virial theorem [21], in which $G(r)$ and $V(r)$ stands for the electronic kinetic energy density (always positive) and electronic potential energy density (always negative), respectively. Thus, negatives values of $\nabla^2\rho(r)$, indicates an excess of electronic potential energy density at BCP in detriment of the kinetic energy, showing a concentration of electronic charge between the nuclei, characterizing a shared interaction [22]. Our values indicate the presence of an IHB with significant covalent character, as considered in the work of Gilli et al. [23]. This fact, for **1a**, can be explained by the resonance assisted hydrogen bond phenomenon (RAHB), where the electron pairs of ester oxygen are in resonance with the carbonyl group, increasing the electron density at the BCP and decreasing the bond length (2.0782 Å). For **4b**, the negative value of the Laplacian in IHB can be also explained by the RAHB phenomenon, where the aromatic ring donates electron density, via resonance, to NO_2 group, causing similar



1a

4b

Fig. 4. Bonding pathways, BCP and contour plots of electronic density for **1a** and **4b**.



3b

4b

Fig. 5. The NBO charge calculated from B3LYP-6-311++G(d,p) to the **3b** and **4b** conformations in gas phase.

effects. However, it is observed that the values of $\nabla^2\rho(r)$ presented here are much smaller than the ones obtained at BCP for common covalent interactions. The AIM calculations on **4b** characterize an IHB involving a seven member ring [24–26], such as the $OH\cdots O \leftarrow N{=}O$.

IR and ^{1}H NMR data have also supported the existence of a seven member ring IHB in **4**. The IR spectroscopic data shows the existence of a broad band corresponding to the O–H stretching ($v = 3472$–$3420\ cm^{-1}$) in **4**, differing from the sharp band obtained for **3** ($v = 3447\ cm^{-1}$). Another spectroscopic feature has been obtained from the ^{1}H NMR data. The tertiary carbinolic hydrogen in **4** appears in a field 0.7 ppm lower than the tertiary carbinolic hydrogen in **3**. This effect can be explained if there is a flow of electron density to the IHB, which does not occur for **3**. The NBO charges [27] were calculated in order to confirm our hypothesis. The atomic charges show that the carbinolic hydrogen in **4b** (+0.208) is more positive than the corresponding hydrogen in **3d** (+0.187). The NBO charges on oxygen in the seven ring IHB of **4b** is −0.412, lower than the corresponding value in **3d** (−0.374). It is interesting to point out that the carbinolic hydrogen in **4b** has a NBO charge similar to a charge expected for aromatic hydrogens. This result is also in agreement with the observed spectroscopic ^{1}H NMR data. Differently, in **3d** there is a large difference between NBO charges of the carbinolic hydrogen and aromatic hydrogens (Fig. 5).

5. Conclusions

In this Letter a new procedure to prepare a new class of bioactive compounds **3** and **4** is presented, along with a corresponding computational and spectroscopic study in gas phase and water media. The efficiency of a RPESS methodology for a rational search of conformers for the aforementioned adducts is also demonstrated, since the most stable anti-periplanar **2d** and **3d** conformations in gas phase were only found using this protocol. The PCM model demonstrated to be important for the relative stabilities of the conformations **1d** and **2d**. AIM calculations and spectroscopic (IR, ^{1}H NMR) data have shown to be complementary in order to characterize intramolecular hydrogen bonds (IHB) in **1** and **4**.

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