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π-π Stacking Interactions of 3a-Aryl-2,3,3a,4-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-ones, X-Ray and DFT Study †

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Abstract: Compounds containing benzimidazole moiety in solid state often demonstrate the ability to the formation of π-π stacking interactions. In this work, we focused on the investigation of intermolecular hydrogen bonds and parallel displaced (PD) π-π stacking interactions found in the crystals of titled molecules, both crystallize with $Z = 2$ in the space group P-1. Differences of the π-π stacking interactions parameters depending on the volume of side aromatic substituent in a homologous series, as well as a theoretical estimation of the energy of these interactions using DFT at two different functionals (M06-2X, MPWB95) and three basis sets [6-31G(d), 6-31++G, and 6-31++G(d)] were shown.

Keywords: 3a-aryl-2,3,3a,4-tetrahydro-1*H*-benzo[*d*]-pyrrolo[1,2-*a*]imidazol-1-ones; stacking interactions; hydrogen bonds; DFT calculations; energy of the stacking interactions

1. Introduction

Molecules of organic compounds often organize themselves in solid state through non-covalent interactions into regular arrangements, or lattices [1]. Hydrogen bonds and weak aromatic interactions play an important role in it. So the understanding of non-covalent interactions between molecules will help in understanding the molecular recognition process.

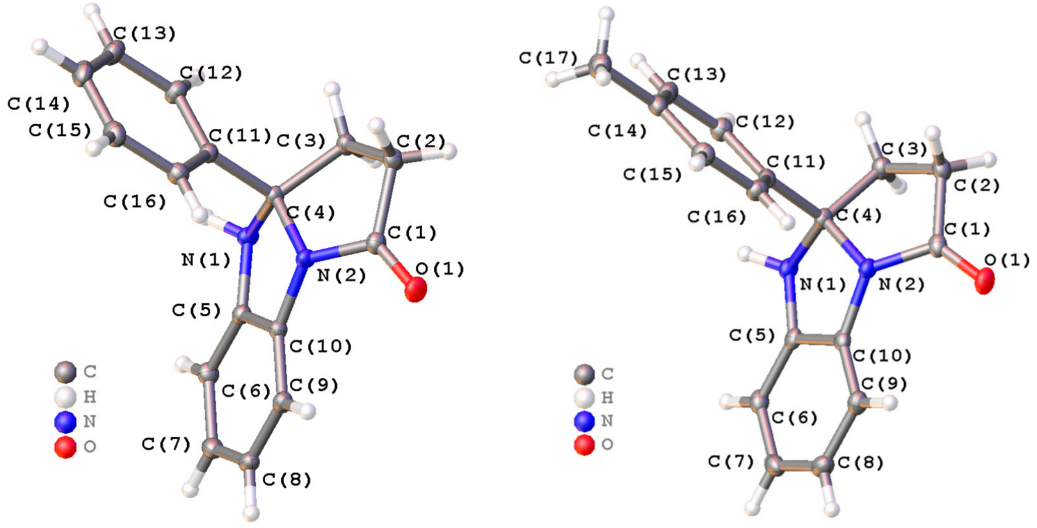
Compounds containing benzimidazole moiety in solid state often demonstrate ability to the formation of π-π stacking interactions. Because these compounds exhibit anticancer activity, DNA-binding research, including theoretical and quantum-mechanical studies, on new complexes containing benzimidazole fragments is very common [2,3] and may lead to the development of a new generation of antitumor drugs.

The structure and some features of compound **1a**, demonstrating plant growth regulating activity, we reported early [4,5].

2. Results

Compounds **1a,b** crystallize with $Z = 2$ in the space group P-1. Crystal structures of **1a,b** with atoms labeling are present on Figure 1. The partly saturated benzimidazole fragment is almost flat, only C(4) atom is going out of the plane, and the torsion angle C(4)–N(2)–C(10)–C(5) is 9.53(9)° and C(5)–N(1)–C(4)–N(2) is 17.45(9)°. Torsion angle N(1)–C(5)–C(10)–N(2) of 1.31(15)° in **1b** slightly less than corresponding one in **1a** [2.08(10)°]. Interatomic distances in benzene ring of this fragment in 1b are 0.001–0.010 Å shorter than those in **1a**. The C(5)–C(10) bond is almost the same in these two structures (the difference is about 0.001 Å), but the other bonds are significantly shorter in **1b**. Small differences in the geometric parameters of the molecules can significantly affect their reactivity. More planar structure and shorter bonds of this fragment may be associated with more pronounced aromaticity of benzimidazole moiety that determines slightly greater reactivity of **1b** than **1a** in S_E reactions. The interatomic distances N(1)–C(5), N(2)–C(10), N(1)–C(4), and N(2)–C(4) in 1b are 0.001–0.004 Å longer than those in 1a and some similar structures, in which the imidazole moieties are unsaturated, and are close to those in structures, where imidazole moieties are completely saturated.

The pyrrolidone ring is non-planar and is in a distorted envelope conformation. The pyrrolidone moieties in compounds **1a** and **2** are also similar. The torsion angle C(1)–C(2)–C(3)–C(4) of compound **1a** with a value of 33.88(9)° is very close to that in compound **2** with a value of 38.6(3)°. The relevant bond lengths of this fragment in compounds **1a** and **2** are not significantly different, except for the N(2)–C(1) bond, which in compound **2** is about 0.02 Å shorter than that in compound **1a**, and they are typical of other pyrrolidone-containing compounds.



(**a**) (**b**)

Figure 1. Crystal structure with atoms labeling of: (**a**) **1a**; (**b**) **1b**. Displacement ellipsoids are drawn at the 50% probability level.

X-ray analysis reveals extensive intermolecular hydrogen bonds between the secondary amino group's hydrogen atom of one molecule and the carbonyl group's oxygen atom of another one. These distances, NH···O=C, are 2.112(17) and 2.20(2) Å for **1a** and **1b**, respectively. Complete parameters of H-bonds given in Table 1.

Table 1. Hydrogen bonds in crystals of 1a and 1b.

Compd	D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
1a	N(1)-H(1N)...O(1) $^{\#1}$	0.914(16)	2.112(17)	2.9994(11)	163.4(14)
1b	N(1)-H(1N)...O(1) $^{\#2}$	0.88(2)	2.20(2)	3.0509(17)	161.2(2)

Symmetry transformations used to generate equivalent atoms: #1: x − 1,y,z; #2: x − 1,y,z.

The hydrogen-bonded chains in **1a,b** are linked by aromatic parallel displaced π-π stacking interactions to form a three-dimensional structure (Figure 2a,b). Important parameters of stacking interactions, such as intercentroid distances, interplanar distances, ring offsets and angle θ, in **1a,b** are shown in Figure 2c.

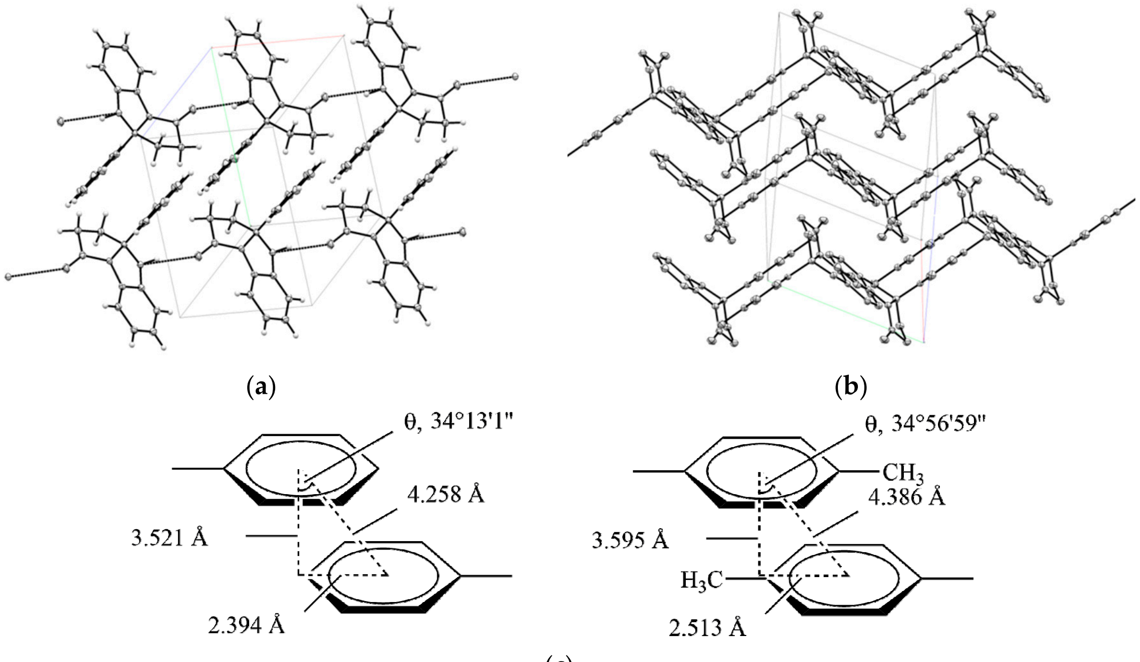


Figure 2. Packing diagrams in projection, showing π-π stacking interactions: (**a**) **1a**; (**b**) **1b**; (**c**) Parameters of stacking in **1a** and **1b**.

3. Discussion

To evaluate the energy of π-π stacking interactions we performed a theoretical study using the DFT quantum-chemical calculations. The π-π stacking is an interaction of electron clouds of two or more aromatic rings, so importance of a method describing accurately non-covalent interactions is obvious. Many popular hybrid functionals like B3LYP not so good describes van der Waals forces. Functionals with dispersion corrections are much more accurate in such cases, so they are often been used for modeling of π-π stacked systems. So, we have chosen M06-2X [6], MPWB95 [7] and the basis sets of 6-31G(d), 6-31++G, and 6-31++G(d), which are common in case of modeling of non-covalent interactions.

To evaluate π-π stacking interactions energy we performed geometry optimization of single molecules and the dimers with the initial geometries obtained from X-ray analysis. The π-π stacking energy was determined using following simple equation:

$$\mathrm{E_{stacking}} = \mathrm{E_{dimer}} - 2 \times \mathrm{E_{monomer}}$$

This equation allows us to compare the energy of the dimeric system in two states: when the distance between the interacting rings corresponds to the minimum of energy and when these rings are infinitely distant from each other.

Table 2. Calculated and experimental intercentroid distances and estimated energies of stacking.

Compd	X-Ray	MPWB95/ 6-31G(d)	MPWB95/ 6-31++G	MPWB95/ 6-31++G(d)	M06-2X/ 6-31G(d)	M06-2X/ 6-31++G	M06-2X/ 6-31++G(d)
1a	4.258	**4.284** [1]	**4.285**	**4.276**	3.938	3.970	3.950
		−4.37 [2]	−4.15	−3.81	−10.42	−10.77	−10.58
1b	4.386	5.246	**4.678**	5.448	4.090	4.094	**4.167**
		−4.40	−3.81	−3.25	−9.25	−9.88	−9.17

[1]: calculated intercentroid distance, (Å); [2]: Energy of stacking (kcal/mol).

Comparing results obtained with the use of different levels of theory we can conclude that M06-2X functional, in general, gives the E_{stacking} significantly greater than MPWB95 (about 3-times) (Table 2). The addition of two diffuse functions to the basis set gives almost no effect. As expected, the E_{stacking}

for **1b** is 1.17–1.41 kcal/mol less than corresponded value for **1a**. To compare the calculated data with corresponding ones obtained from X-ray we can choose an intercentroid distance as a criterion of correctness of calculations. As it can be seen M06-2X functional overestimates of E_{stacking}: intercentroid distances are smaller than corresponding ones obtained from X-ray, especially for **1a**. Only in case of M06-2X/6-31++G(d) level of theory the intercentroid distance for **1b** is quite close to the corresponding value from X-ray, but the E_{stacking} is still enormous (−9.17 kcal/mol).

In case of MPWB95/6-31++G we obtained the best agreement with the X-ray data values for both intercentroid distances in **1a** and **1b**—4.285 and 4.678 Å, respectively (compare to those from X-ray, 4.258 and 4.386 Å, see Table 2).

4. Materials and Methods

4.1. Synthesis of the Compounds

3a-Phenyl-2,3,3a,4-tetrahydro-1*H*-benzo[*d*]-pyrrolo[1,2-*a*]imidazol-1-one (**1a**). A solution of 2 g (11 mmol) of 4-oxo-4-phenylbutanoic acid and 1.2 g (11 mmol) of 1,2-phenylenediamine in 30 mL of anhydrous benzene was boiled while continuously distilling off the azeotropic mixture with formed water over 5 h. After being left to stand overnight, the separated crystals or precipitate was washed with benzene and then with *n*-hexane. If necessary, it may be recrystallized from acetone. Yield 2.12 g (75%), light-yellow crystals, mp 156–159 °C. IR spectrum, ν, cm^{-1}: 3330 (NH), 1710 (C=O, "Amide-I"), 1320 (C–N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.35–2.60 m (2H, C^3H_2 pyrrolidine), 2.70–2.90 m (2H, C^2H_2 pyrrolidine), 4.38 s (1H, NH), 6.50–6.90 m (4H aromatic), 7.25–7.60 m (5H aromatic, Ph). Found, %: C 76.56; H 5.73; N 11.56. $C_{16}H_{14}N_2O$. Calculated, %: C 76.80; H 5.60; N 11.20.

3a-(4-Methylphenyl)-2,3,3a,4-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-one (**1b**). Yield 1.98 g (78%), light-yellow crystals, mp 158–160 °C. IR spectrum, ν, cm^{-1}: 3350 (NH), 1690 (C=O, "Amide-I"), 1330 (C–N). ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 2.40–2.55 m (2H, C^3H_2 pyrrolidine), 2.50–2.70 m (2H, C^2H_2 pyrrolidine), 4.35 s (1H, NH), 6.50–6.85 m (4H aromatic), 7.15–7.35 d.d (4H aromatic). Found, %: C 76.16; H 6.15; N 10.10. $C_{17}H_{16}N_2O$. Calculated, %: C 75.69; H 6.06; N 10.61.

4.2. X-ray Study

X-ray diffraction was performed on an Bruker *SMART* 1000 CCD area-detector diffractometer (graphite monochromator, λ(Mo$K\alpha$) = 0.71073 Å, ω scan) at 100 K. The structures were solved by a direct method and was refined by full-matrix least-squares versus F^2_{hkl} with anisotropic displacement parameters for all non-hydrogen atoms. The N-bound H atom was located from a Fourier difference synthesis and refined isotropically. C-bound H atoms were refined as riding, with methylene C—H = 0.99 Å and aryl C—H = 0.95 Å, and with U_{iso}(H) = 1.2 U_{eq}(C). Solving and refinement were carried out using the SHELX software package (ver. 5.1) [8]. The overlays and packing diagrams as well as parameters of non-covalent interactions were obtained using Olex2 software (ver. 1.2.8) [9].

4.3. DFT Study

All DFT calculations were performed using Gaussian 09 package [10]. Coordinates from X-ray data were used as initial and full geometry optimization of monomers and dimers were performed using MPWB95 and M06-2X functionals with 6-31G(d), 6-31++G, and 6-31++G(d) basis sets.

Author Contributions: V.G. carried out the synthesis of reported compounds and obtained the single crystals, took part in the spectral characterization of synthesized compounds, performed DFT calculations, drafted the manuscript, prepared final version of the manuscript, A.Y. designed and supervised all experiments, and manuscript drafting. All authors read and approved the final version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

MDPI	Multidisciplinary Digital Publishing Institute
DOAJ	Directory of open access journals
CCDC	The Cambridge Crystallographic Data Centre
PD	Parallel displaced
RFBR	Russian Foundation for Basic Research
S_E	Electrophilic substitution reactions

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