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Molecular structure and conformational analysis of two 2-oxo(thioxo)-1,2,3,4-tetrahydropyrimidine-5-esters

Hamid Reza Memarian [a,*], Mahnaz Ranjbar [a], Hassan Sabzyan [a], Mohammad Hossein Habibi [a], Takayoshi Suzuki [b]

[a] Department of Chemistry, University of Isfahan, Isfahan 81746-73441, Islamic Republic of Iran
[b] Department of Chemistry, Okayama University, Tsushima-naka 3-1,1, Okayama 700-8530, Japan

HIGHLIGHTS

- X-ray and DFT data of two 2-oxo(thioxo)-1,2,3,4-tetrahydropyrimidines are analyzed.
- They appeared as racemic mixtures with pseudo-axial orientation of C_4 aryl group.
- DFT result of one compound indicates different orientation of the CO ester group.
- Intermolecular interaction between the Br atom and hydrogen bond donor is observed.

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ABSTRACT

X-ray crystal structure analysis and quantum chemical calculations based on density functional theory (DFT) were used for structural and electronic characterizations of two 1,2,3,4-tetrahydropyrimidine derivatives (THPMs), namely, ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**) and methyl 4-(4-bromophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**). The results of these studies revealed that the heterocyclic ring adopts a *quasi-boat* conformation, in which the 4-aryl group occupies the *pseudo-axial* position. The occurrence of the C_4-stereocenter in the heterocyclic ring causes the formation of both *R*- and *S*-enantiomers. X-ray diffraction technique indicates that both compounds exist as a racemic mixture in the crystal structure and the enantiomers are orientated to each other *via* hydrogen bonding between N_3—H as donor and the C_2=S or C_2=O groups as acceptor species, in each layer under formation of an *enantio-syndio* packing. Most computational bond lengths and angles are well in agreement with experimental data, and support the *pseudo-axial* orientation of the C_4-aryl substitution.

1. Introduction

2-Oxo-1,2,3,4-tetrahydropyrimidines (THPMs), also known as Biginelli compounds [1], have important therapeutic and pharmacological properties, as calcium-channel blockers [2], antihypertensive agents [3], HIV gp-120-CD4 inhibitors [4], and showing antitumor [5], antibacterial [6] and anti-inflammatory [7] activities. X-ray crystal structure analysis and computational studies of these compounds revealed that THPMs adopt a *pseudo-boat* conformation of the six-member heterocyclic ring with a *pseudo-axial* orientation of the C_4-substituent [8–16]. To the best of our knowledge there is no report on the *pseudo-equatorial* arrangement of C_4-substituent. THPMs are asymmetric molecules and the influence of the absolute configuration at the stereogenic center at C_4 atom and the orientation of 5-CO group with respect to C_5=C_6 double bond on the biological activity is well documented [17]. The results revealed that calcium channel modulation of THPMs is dependent on the absolute configuration at C_4, whereby the orientation of the 4-aryl group (*R- vs. S*-enantiomer) acts as a "molecular switch" between antagonist and agonist activity [17,18]. Keeping this statement in mind that only THPMs with *R* configuration show antagonist activity, we were interested in knowing the reason of failing the formation of *S*-enantiomer with *pseudo-equatorial* orientation of C_4-aryl group. In our recent study we discussed the possible formation of the enantiomeric forms and analyzed the structural parameters especially the energy content of each enantiomers [19].

Due to the presence of C_4-stereocenter in THPMs, it is expected that two possible enantiomeric pairs **A**/**B** [(*R*)-Ar-ax/(*S*)-Ar-eq] and **C**/**D** [(*S*)-Ar-ax/(*R*)-Ar-eq] depending on the space orientation of the

* Corresponding author. Tel.: +98 311 7932707; fax: +98 311 6689732.
E-mail addresses: memarian@sci.ui.ac.ir, hrmemarian@yahoo.com (H.R. Memarian).

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aromatic ring could be formed (Fig. 1). These structures should be considered in the structural and stability analyses, especially the intermolecular interaction between the enantiomers either in the (computational) gas phase or (solid state) X-ray crystal structures. The important point in this study was to elucidate the preferred axial or equatorial orientations of C_4 substituent on the heterocyclic ring. As is shown in Fig. 1, in the enantiomeric pair **A**/**B**, the formal displacement of the aryl group from axial Ar-ax (**A**) towards equatorial position Ar-eq (**B**), leads to the formation of the *S*-enantiomer, while reflecting the overall molecule with respect to the plane passing through the ring containing both N_1 and C_4 atoms (formal displacement of N_3/C_5 atoms with their substituents), produce the *S*-enantiomer **C**, in which the aryl group remains in its axial position. The same can be said for the enantiomeric pair **C**/**D**. Since the THPM with *R* configuration is only the suitable candidate as calcium channel modulator, two isomers (*R*)-Ar-ax (**A**) or (*R*)-Ar-eq (**D**) are expected to have this biological activity.

The results of DFT study at B3LYP/6-31++G** level on various substituted THPMs [19] has indicated that:

i. C_4-aryl substituent in both *R*- and *S*-enantiomers occupies *pseudo-axial* position (Fig. 1, Types **A** and **C**) and as expected with equal energy content.
ii. Ring flip calculation carried out on C_4-phenyl substituent in *pseudo-axial* position ((*R*)-Ar-ax; Fig. 1, type **A**) as representative bringing this substituent in *pseudo-equatorial* position ((*R*)-Ar-eq; Fig. 1, type **D**) increases the energy content of this structure *ca.* 9 kJ/mol. This can be attributed possibly to the increased steric effect (gauche interaction) of the phenyl substituent with C_5-carboethoxy group (Fig. 2).

The aims of the present study were to compare the structural data concerning bond lengths and angles, and rings orientation obtained from DFT study of two THPM compounds with those obtained from their X-ray crystal structural analyses. Due to importance of the intermolecular interaction, suitable crystal of N_1-unsubstituted THPM, ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**) and N_1-substituted THPM, methyl 4-(4-bromophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**), as presented in Fig. 3, were considered for this study.

2. Experimental section

2.1. Crystal structure determination of compounds *1* and *2*

The compounds **1** and **2** are synthesised by the procedure reported earlier [20], and were recrystallised from ethanol and *n*-hexane/ethyl acetate, respectively. Single crystals of these compounds with suitable size for X-ray diffraction are selected and all measurements are made on a Rigaku RAXIS RAPID imaging plate area detector. Structures of target compounds are visualized in MERCURY software medium. The details of the crystal data of these compounds and refinement are given in Table 1.

2.2. Computational methods

Structures of compounds **1** and **2** were built and optimized preliminarily with semi-empirical PM3 method using HyperChem software [21]. These PM3 optimized structures were used as initial guess geometries for the *ab initio* calculations. Geometry optimization of compounds **1** and **2** are performed with B3LYP density functional level of theory (DFT) in conjunction with 6-31++G** basis set using Gaussian 98 program package [22].

3. Results and discussion

3.1. Structural analysis

The solid-state structures of compounds **1** and **2** are shown in Fig. 3. The compound **1** crystallizes in a triclinic crystal system

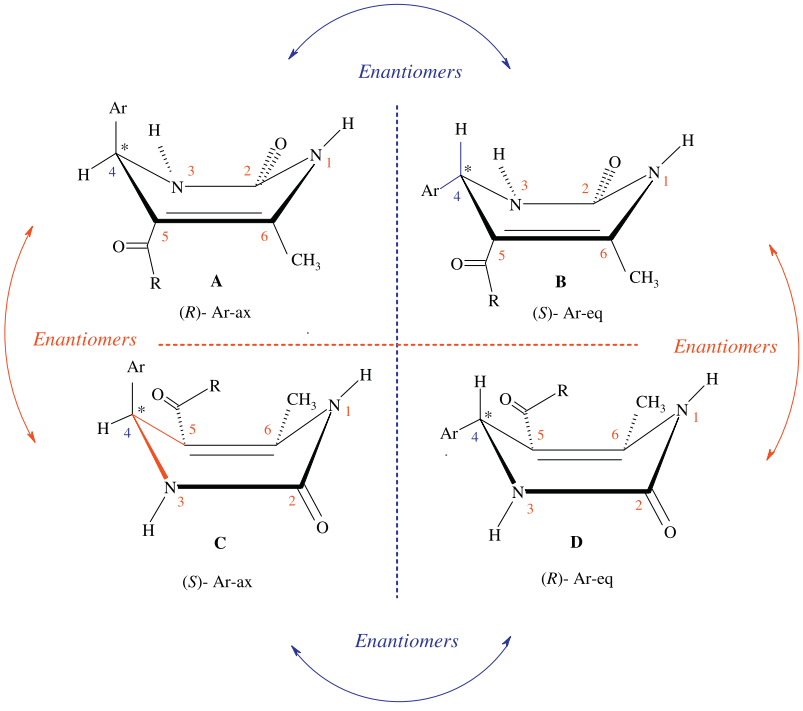

Fig. 1. Different enantiomeric forms for THPMs depending on the space orientation of the aryl group.