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Synthesis, crystal structure and theoretical study of two isomeric poly-substituted derivatives of 1,4-dihydropyridine

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1,4-Dihydropyridines are well known as an important class of calcium-channel blockers with wide clinical usage as antihypertensive agents. They have very interesting spectral and chemical properties, which are investigated experimentally and theoretically. Two isomeric poly-substituted 1,4-dihydropyridines were synthesized by three different one-step synthetic schemes. The structures of diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**I**) and diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**II**) were characterized by melting point, elemental analysis, IR and UV-Vis spectroscopy. Their structures were confirmed by X-Ray crystallography. The compound **(I)** crystallizes in a monoclinic system, space group $P2_1/c$, a = 739.1(1), b = 2769.5(3), c = 880.9(1) Å, α = 104.24(2) º, $\beta = \gamma$ = 90º, Z = 4, V = 1.7476(4) Å ^{3}. The compound **(II)** crystallizes triclinic, space group $P\bar{1}$, a = 742.8(1), b = 894.2(2), c = 1407.5(2) Å, α = 80.23(2) º, β = 86.86(2)^0, γ = 68.71(2)º, Z = 2, V = 0.8584(3) Å ^{3}. The spectral behavior of the optimized structures of these compounds was reproduced by the hybrid DFT method B3LYP and HF method both with 6-31G basis set and some semi-empirical methods for comparison. The theoretical spectra were compared with the experimental ones.

Key words: 1,4-Dihydropyridines; Synthesis; X-Ray Diffraction Analysis; DFT, HF, AM1 and PM3 Study; UV-Vis and IR spectra.

INTRODUCTION

The nucleus of 1,4-dihydropyridine (1,4-DHP) is an important scaffold for calcium channel antagonism and other cardiovascular activities [1-5]. The structural requirement for such antihypertensive and antianginal properties has the envisaged importance of electron-withdrawing groups at a *meta* substituted phenyl ring, attached to the C4 of 1,4-DHP rings. Most of the known DHP drugs have symmetrical, as well as asymmetric structures with respect to the C3 and C5 positions. The *m*-NO_2 phenyl 1,4-DHPs were well-explored to obtain *Nimodipine*, *Nitrenedipine*, *Cilnidipine*, *Manidipine*, *Barnidipine* and *Efonidipine*. Along with well known cardiovascular effects of DHPs, there are additional data for antiinflammatory effects [6], antioxidant activity [7], K_{ATP} channel activation activity [8], and atheroprotective effects [9]. Some DHPs have influence on rat paw edema [10]. The hydroxyl group as a substituent has not been well-explored in such DHP systems.

There are many different literature data about Hantzsch reaction [11–15]. Some of them, which we used, give good yields and purity of the resulting compounds, the reaction time is reduced in comparison with the classical type of the reaction and reaction conditions are in agreement with international conventions of green chemistry.

The crystal structures of hydroxyl substituted DHPs are not described in the literature until now. For this reason it was interesting to confirm the supposed structure, because our previous investigations showed that not every arylaldehyde reacts successfully in Hantzsch reaction and in many cases other products are obtained instead of 1,4-DHPs.

The literature data show the good prediction ability of quantum mechanics methods (*ab initio* and semi-empirical) by optimization of molecular geometry and calculation of UV-Vis and IR spectra and some physicochemical properties of 1,4-DHPs [16–19].

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EXPERIMENTAL

Materials and Methods

All starting materials were purchased from Merck and Sigma-Aldrich and were reagent grade. They were used without further purification. Melting points were measured in open capillary tubes on a Büchi 535 melting point apparatus. The elemental analysis was realized by atomic absorption spectrometry. The UV-Vis spectra were taken on a Hewlett-Packard 8452A UV-Vis spectrophotometer with a step of 2 nm, scanning speed of 1 s/spectrum with diode-array detector and quartz test tube of 1 cm thickness. The spectra were obtained in ethanol solutions against ethanol as a blank sample. The IR spectra were recorded on a FTIR Perkin-Elmer spectrometer in KBr tablets and frequencies were expressed in cm^{-1}.

General Procedures for the Preparation of 1,4-Dihydropyridines

The compounds diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (I) and its isomer diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4,-dihydropyridine-3,5-dicarboxylate (II) (Fig. 1) were synthesized by the:

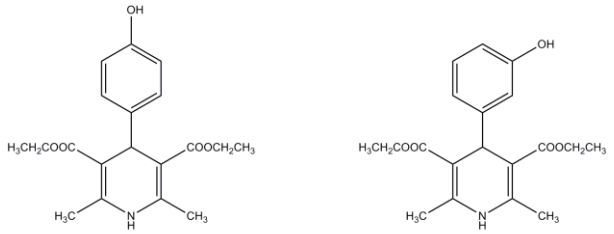

Fig. 1. Chemical Structures of diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (I) and diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (II)

Experimental Procedure 1 (P1):

A reaction mixture of 3-, resp. 4-hydroxybenzaldehyde (1.22 g, 10 mmol) and ethyl acetoacetate (2.60 g, 20 mmol) was heated in ethanol under reflux until boiling. Then NH_3 (3 mL) was added and the mixture was heated for 5 h. After the end of the reaction distilled water (40 mL) was added to the mixture (slowly and carefully). After cooling a yellow precipitate was obtained. The precipitate was recrystallized.

Experimental Procedure 2 (P2):

A reaction mixture of 3-, resp. 4-hydroxybenzaldehyde (1.22 g, 10 mmol), ethyl acetoacetate (2.60 g, 20 mmol) and ammonium acetate (0.77 g, 10 mmol) was heated in water medium under reflux until a yellow precipitate was obtained (1.5 h). The precipitate was recrystallized from an appropriate solvent.

Synthesis of diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Yellow crystals, m.p. 231.8-233.7^{0}C (methanol); Yield (P1, P2): 1.82 g (53 %), 3.0 g (87 %); FTIR (KBr): $\bar{\nu}$ = 3352, 3308, 1650, 1595, 1473, 1368, 1218, 1128, 1019 cm^{-1}; UV–Vis (EtOH): λ_{max} = 220, 272, 320, 374 nm; Anal.: $C_{19}H_{23}NO_5$ (345.38), calcd. % C 66.07, % H 6.71, % N 4.06, found % C 66.53, % H 6.49, % N 4.17.

Synthesis of diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Yellow crystals, m.p. 185.8-187.0 ^{0}C (2-propanol); Yield (P1, P2): 1.78 g (52 %), 2.98 g (86 %); FTIR (KBr): $\bar{\nu}$ = 3347, 1662, 1591, 1488, 1369, 1226, 1130, 1021 cm^{-1}; UV-Vis (EtOH): λ_{max} = 220, 274, 320, 376 nm; Anal.: $C_{19}H_{23}NO_5$ (345.38), calcd. % C 66.07, % H 6.71, % N 4.06, found % C 66.54, % H 6.67, % N 4.11.

X-Ray Crystal Structure Analyses

The crystal structures of the compounds were determined by single crystal X-Ray diffraction. Data collection was carried out at -40 ^{0}C on an IPDS single crystal diffractometer (STOE, Darmstadt) using graphite-monochromated MoK_α radiation. The structures were solved by direct methods with the program SHELXS and refined with SHELXL, both from the SHELXL-97 program package [20]. All atom positions, including those of hydrogen atoms were localized from the electron density map. All non-hydrogen atoms were afterwards refined anisotropically.

Complete data collection parameters and details of the structures solutions and refinements are given in Table 1. The plots of the molecular structures were produced using the DIAMOND program (ver. 3.1) (CRYSTAL IMPACT GbR, Bonn, Germany).

Data of the crystal structures can be obtained from Cambridge Crystallographic Data Centre (CCDC number 701877 (I) and CCDC number 701878 (II)) free of charge via www.ccdc.cam.ac.uk/products/csd/request/.

METHODS OF COMPUTATION

All the calculations were performed on a single processor computer. Gaussian 03 (Frisch et al.) [21] software package was used for structure

Table 1. Crystal data and structure refinement for the two isomeric 1,4-dihydropyridines

Identification code	I	II
Chemical formula	$C_{19}H_{23}NO_5$	$C_{19}H_{23}NO_5$
Formula weight	345.38	345.38
Temperature [K]	230(2)	235(2)
Crystal system	monoclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$
Unit cell dimension	a = 739.0(1) pm; $\alpha = 90^0$ b = 2769.5(3) pm $\beta = 104.24(2)^0$ c = 880.9(1) pm; $\gamma = 90^0$	a = 742.8(1) pm; $\alpha = 80.23(2)^0$ b = 894.2(2) pm $\beta = 86.86(2)^0$ c = 1407.5(2) pm; $\gamma = 68.71(2)^0$
Cell volume [nm^3]	1.7475(4)	0.8584(2)
Z	4	2
Density (calculated) [g cm^{-3}]	1.313	1.336
Radiation type	Mo K_α	Mo K_α
Wavelength [pm]	71.073	71.073
Absorption coefficient [mm^{-1}]	0.095	0.097
F(000)	736	368
Crystal description	colorless block	colorless block
Crystal size [mm^3]	0.4 × 0.3 × 0.45	0.45 × 0.3 × 0.3
Reflections collected	15146	8577
Independent reflections	3054 [R(int) = 0.0393]	2798 [R(int) = 0.0482]
Reflections observed [$I > 2\sigma(I)$]	2325	2176
θ range for data collection [deg]	2.50 to 24.94	2.48 to 25.88
Index ranges	$-8 \le h \le 8$, $-32 \le k \le 32$, $-10 \le l \le 10$	$-8 \le h \le 8$, $-10 \le k \le 10$, $-15 \le l \le 15$
Data / parameters	3054 / 318	2798 / 318
Goodness-of-fit on F^2	0.959	1.059
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0361; $wR2$ = 0.0898	$R1$ = 0.0587; $wR2$ = 0.1361
Final R indices (all data)	$R1$ = 0.0482; $wR2$ = 0.0949	$R1$ = 0.0779; $wR2$ = 0.1450
$(\Delta/\rho)_{max}$ [$e.Å^{-3}$]	0.267	0.246
$(\Delta/\rho)_{min}$ [$e.Å^{-3}$]	-0.184	-0.220
Measurement	STOE IPDS I	STOE IPDS I
Structure determination	SHELX-97	SHELX-97
Refinement	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2

optimization and spectral behavior calculation. GaussView and ChemBio3D programs were utilized for visualization of all spectra. The hybrid DFT method B3LYP and RHF both with 6-31G basis set and some semi-empirical methods (AM1 and PM3) were used for geometry optimization and calculation of spectral and other properties.

RESULTS AND DISCUSSION

Chemistry

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The corresponding two isomeric compounds were synthesized via classical type of Hantzsch reaction under two different reaction conditions. We found some serious advantages of using water as reaction medium in contrast to ethanol. The reaction time was vastly reduced (about 3.5 times); the end of the reaction was visually detected – when the reaction was completed, a precipitate of the target compound was obtained, because of its low solubility in water. The resulting yield was about 30 % higher. Using of water is also in good agreement with the principles of green chemistry. The synthesized compounds were characterized by elemental analysis, IR and UV-Vis spectrometry and single crystal X-Ray diffractometry. The analytical data confirmed our hypothesis about the structure of I and II.

Crystal Structure

Colorless block-like crystals suitable for X-Ray diffraction analysis were grown by slow evaporation of a methanol, resp. 2-propanol solution of the corresponding compounds. Crystallographic data of the investigated crystals are listed in Table 1. The solid state structures of a molecule of the compounds (I) and (II) are shown in Figs. 2 and 3, respectively.

By comparison of the experimental data for (I) and (II) with the data for other similar compounds

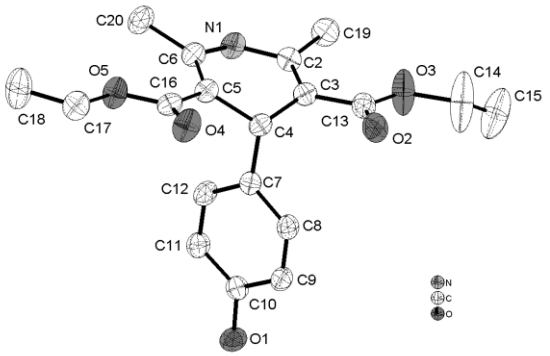

Fig. 2. Crystal structure of diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (I) (displacement ellipsoids for C and O with 50 % probability). (DIAMOND plot)

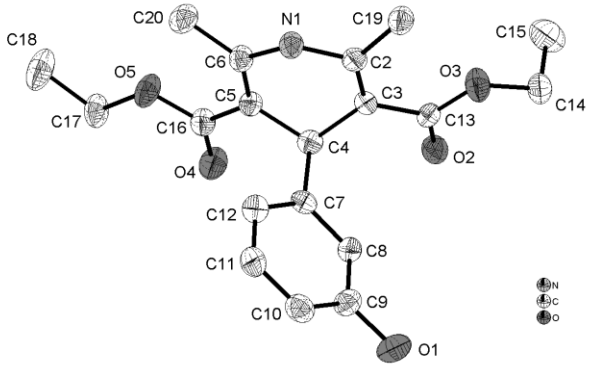

Fig. 3. Crystal structure of diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (II) (displacement ellipsoids for C and O with 50 % probability). (DIAMOND plot

[22] it can be stated that most of the bond lengths and angles for the described compounds agree very well with the standard values.

The 1,4-dihydropyridine rings have an expected flat boat conformation, with N1 and C4 at a distance of 277.1 Å (I) and 274.8 Å (II) through the four carbon atoms (C2, C3, C5 and C6), which define the base of the boat. The degree of ring distortions at N1 and C4 is directly reflected in the magnitude of the torsion angles emanating from these two atoms. The torsion-angle values of C2-C3-C4-C5: -30.99(1)^0 (I) and 35.20(1)º (II) or C3-C4-C5-C6 28.60(1)º (I) and -33.11(1)º (II) are higher in the DHP ring, which indicates that puckering is greater at C4 than at N1.

The structures have intra- and intermolecular hydrogen bonds of the type C-H---O, N-H---O and O-H---O, which help to stabilize the crystal structures. Every molecule is linked with other molecules into infinite chains by intermolecular hydrogen bonds between the amine H atom of a molecule and the carbonyl oxygen of a neighbouring molecule or between the hydroxyl H atom of a molecule and the carbonyl oxygen of a neighbouring molecule.

THEORETICAL PART

Structure

Because the crystal structures of the two corresponding 1,4-DHPs were known, we wanted to check the correlation between X-Ray data and theoretical calculations. To this aim we generated theoretical models of (I) and (II) (ChemBio3D software package) and after molecular mechanics optimization of the structures using MM2 force field, full optimization of the molecular geometry was done *via* different *ab initio* (DFT and HF both with 6-31G basis set) and semi-empirical (AM1 and PM3) methods for comparison.

The calculated and selected bond lengths for I and II are given in Tables 2 and 3. The calculated and selected bond angles for I and II are given in Tables 4 and 5. There is a very good correlation between experimental and calculated values of bond lengths and angles, especially for I using the DFT B3LYP method which finds very broad usage in this kind of calculations. The molecular geometry parameters are very close to the data for other similar structures like diethyl 4-(3-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate [22]. As a rule, the results obtained with semi-empirical methods are with bigger diversion from the experimental values of molecular geometry parameters, but these methods are vastly faster than *ab initio*. It may be concluded that DFT and HF methods with 6–31G basis set are appropriate for geometry optimization of the 1,4-DHPs.

UV-Vis Spectra

The excitation states of the corresponding compounds were calculated for singlet state and half-singlet / half-triplet state by B3LYP and RHF methods using a 6-31G basis set (Table 6). The values for λ_{max} obtained from hybrid DFT method B3LYP were higher than the HF values and there is very good approximation with some of the maxima in the experimental ones, especially for I (320 nm). All maxima obtained from the experiment or quantum mechanical calculations for the two compounds are very similar because of their similar structure. The reasons for some disagreements between experimental and theoretical data could be the specifics of the calculation methods or the fact that the experimental spectra were obtained in 95%

Table 2. Selected bond lengths [Å] for diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (I).

	X-Ray	B3LYP (6-31G)	HF (6-31G)	AM1	PM3
N 1 – C 2	137.7(2)	139.5(6)	138.5(7)	139.5(7)	143.2(3)
N 1 – C 6	138.2(2)	139.5(6)	138.5(7)	139.5(7)	143.2(3)
C 2 – C 3	135.9(2)	136.5(3)	134.4(1)	136.8(7)	135.0(1)
C 2 – C 19	150.4(2)	150.9(8)	150.8(5)	149.5(1)	149.1(2)
C 3 – C 13	146.6(2)	146.1(9)	146.1(7)	146.2(1)	148.9(5)
C 3 – C 4	151.9(2)	153.0(5)	152.3(6)	150.5(4)	150.4(2)
C 4 – C 5	151.5(2)	153.0(5)	152.3(6)	150.1(7)	150.4(2)
C 4 – C 7	153.0(2)	153.7(2)	153.2(1)	150.5(1)	151.0(3)
C 5 – C 6	135.3(2)	136.5(3)	134.4(1)	136.7(1)	135.0(1)
C 5 – C 16	147.1(2)	146.1(9)	146.1(7)	146.4(5)	148.9(5)
C 6 – C 20	149.8(2)	150.9(8)	150.8(6)	149.5(2)	149.1(2)
C 10 – O 1	136.2(8)	139.6(1)	138.0(1)	137.7(3)	136.8(4)
C 13 – O 2	121.1(2)	124.5(4)	122.1(1)	123.7(1)	121.5(7)
C 13 – O 3	132.0(2)	138.9(1)	135.1(7)	137.3(3)	136.4(2)
C 14 – O 3	145.8(2)	147.8(5)	145.4(5)	143.9(3)	142.9(1)
C 14 – C 15	135.8(4)	151.8(1)	151.2(1)	150.9(3)	151.6(6)
C 16 – O 4	121.0(2)	124.5(4)	122.1(1)	123.4(9)	121.5(7)
C 16 – O 5	133.5(2)	138.9(1)	135.1(7)	137.3(5)	136.4(2)
C 17 – O 5	145.5(2)	147.8(5)	145.4(5)	143.9(1)	142.9(1)
C 17 – C 18	148.2(2)	151.8(1)	151.2(1)	150.9(3)	151.6(6)

Table 3. Selected bond lengths [Å] for diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (II).

	X-Ray	B3LYP (6-31G)	HF (6-31G)	AM1	PM3
N 1 – C 2	139.1(2)	139.6(2)	138.3(1)	139.6(6)	143.1(8)
N 1 – C 6	138.5(2)	139.4(2)	138.5(1)	139.5(6)	143.1(8)
C 2 – C 3	135.1(2)	136.5(6)	134.5(5)	136.8(3)	135.0(6)
C 2 – C 19	150.0(2)	150.6(7)	150.6(9)	149.5(1)	149.1(2)
C 3 – C 13	146.5(2)	146.8(4)	146.0(3)	146.3(4)	149.0(1)
C 3 – C 4	152.9(2)	152.9(1)	152.1(4)	150.4(7)	150.3(8)
C 4 – C 5	149.0(3)	153.4(6)	152.6(4)	150.1(6)	150.3(8)
C 4 – C 7	154.0(2)	154.1(4)	153.4(5)	150.7(3)	151.2(2)
C 5 – C 6	136.4(2)	136.6(1)	134.4(9)	136.7(5)	135.0(6)
C 5 – C 16	147.2(2)	146.0(5)	146.1(5)	146.4(9)	149.0(1)
C 6 – C 20	149.0(3)	150.9(5)	150.8(7)	149.5(2)	149.1(2)
C 9 – O 1	137.0(2)	139.5(9)	137.9(5)	137.7(8)	136.9(7)
C 13 – O 2	121.8(2)	124.9(4)	122.6(6)	123.6(1)	121.4(5)
C 13 – O 3	133.2(2)	138.2(1)	134.4(4)	137.3(6)	136.9(1)
C 14 – O 3	143.9(2)	147.8(1)	145.3(5)	143.5(2)	142.2(1)
C 14 – C 15	149.5(3)	152.2(8)	151.6(4)	150.8(7)	151.7(1)
C 16 – O 4	121.7(2)	124.6(5)	122.1(6)	123.4(5)	121.4(5)
C 16 – O 5	133.3(2)	138.9(6)	135.1(3)	137.4(2)	136.9(1)
C 17 – O 5	146.3(2)	148.1(3)	145.6(6)	143.4(8)	142.2(1)
C 17 – C 18	148.5(4)	152.2(6)	151.6(4)	150.8(7)	151.7(1)

ethanol solutions (10^{-3} M) in contrast to theoretical, which were produced in solid state.

The excited states for half singlets and half triplets ("50-50") are very close to the experimental data, especially at λ_{max} = 320. These electronic transitions were with lower energy, because of the lower energy of the B3LYP virtual orbitals. The higher maxima obtained with the HF method are very close to the experimental ones.

The absorption maximum at λ_{max} = 220 nm both for I and II corresponds to aromatic double bonds from aryl ring at C4 position, which take part in π --> π^* transitions. Ester C=O groups absorb energy at 272 and 274 nm (n --> π^* transitions) for I and II, respectively. The absorption maximum at 320 nm corresponds to the transition of O-H group in the aryl ring of the compounds. The compound I has more intensive absorption than II.

Table 4. Selected angles [°] for diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (I).

	X-Ray	B3LYP(6-31G)	HF(6-31G)	AM1	PM3
C 2 – N 1 – C 6	123.9(1)	124.6(1)	124.3(1)	120.7(1)	118.0(1)
C 3 – C 2 – N 1	118.2(1)	118.4(1)	118.6(1)	120.1(1)	120.0(1)
C 3 – C 2 – C 19	128.6(1)	127.9(1)	128.1(1)	122.9(1)	124.6(1)
N 1 – C 2 – C 19	113.1(1)	113.7(1)	113.3(1)	117.0(1)	115.4(1)
C 2 – C 3 – C 13	125.7(1)	125.2(1)	124.6(1)	124.4(1)	122.2(1)
C 2 – C 3 – C 4	119.5(1)	120.8(1)	121.1(1)	121.4(1)	122.7(1)
C 13 – C 3 – C 4	114.8(1)	114.1(1)	114.3(1)	114.1(1)	115.0(1)
C 5 – C 4 – C 3	110.7(1)	111.3(1)	111.0(1)	111.2(1)	111.6(1)
C 5 – C 4 – C 7	112.0(1)	111.6(1)	111.6(1)	111.5(1)	110.8(1)
C 3 – C 4 – C 7	109.6(1)	111.6(1)	111.6(1)	110.3(1)	110.8(1)
C 6 – C 5 – C 16	125.4(1)	125.2(1)	124.6(1)	123.8(1)	122.2(1)
C 6 – C 5 – C 4	119.8(1)	120.8(1)	121.1(1)	121.7(1)	122.7(1)
C 16 – C 5 – C 4	114.6(1)	114.1(1)	114.3(1)	114.5(1)	115.0(1)
C 5 – C 6 – N 1	118.6(1)	118.4(1)	118.6(1)	120.0(1)	120.0(1)
C 5 – C 6 – C 20	128.3(1)	127.9(1)	128.1(1)	122.7(1)	124.6(1)
N 1 – C 6 – C 20	113.2(1)	113.7(1)	113.3(1)	117.3(1)	115.4(1)
C 8 – C 7 – C 4	120.8(1)	121.4(1)	121.5(1)	121.7(1)	121.2(1)
C 12 – C 7 – C 4	121.7(1)	120.3(1)	120.5(1)	119.0(1)	119.2(1)
O 1 – C 10 – C 11	122.6(1)	122.8(1)	122.6(1)	122.7(1)	123.0(1)
O 1 – C 10 – C 9	118.0(1)	117.0(1)	117.1(1)	116.6(1)	116.2(1)
O 2 – C 13 – O 3	121.7(1)	120.6(1)	120.3(1)	116.7(1)	119.7(1)
O 2 – C 13 – C 3	122.4(1)	123.9(1)	123.5(1)	127.3(1)	127.1(1)
O 3 – C 13 – C 3	115.9(1)	115.5(1)	116.2(1)	116.0(1)	113.2(1)
C 13 – O 3 – C 14	116.8(2)	116.1(1)	119.2(1)	116.2(1)	118.3(1)
C 15 – C 14 – O 3	111.7(2)	106.9(1)	106.9(1)	106.3(1)	106.4(1)
O 4 – C 16 – O 5	122.1(1)	120.6(1)	120.3(1)	117.1(1)	119.7(1)
O 4 – C 16 – C 5	123.7(1)	123.9(1)	123.5(1)	127.6(1)	127.1(1)
O 5 – C 16 – C 5	114.2(1)	115.5(1)	116.2(1)	115.3(1)	113.2(1)
C 16 – O 5 – C 17	117.0(1)	116.1(1)	119.2(1)	116.1(1)	118.3(1)
O 5 – C 17 – C 18	107.3(1)	106.9(1)	106.9(1)	106.3(1)	106.4(1)

Table 5. Selected angles [°] for diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (II).

	X-Ray	B3LYP(6-31G)	HF(6-31G)	AM1	PM3
C 2 – N 1 – C 6	123.2(2)	124.5	124.1	120.6	118.0
C 3 – C 2 – N 1	117.4(2)	118.8	119.0	120.1	120.0
C 3 – C 2 – C 19	129.7(2)	127.9	126.8	122.8	124.5
N 1 – C 2 – C 19	112.8(2)	113.3	114.1	117.1	115.5
C 2 – C 3 – C 13	124.6(2)	121.8	120.4	124.3	121.4
C 2 – C 3 – C 4	119.1(2)	120.3	121.2	121.4	122.7
C 13 – C 3 – C 4	116.3(1)	117.8	118.4	114.2	115.9
C 5 – C 4 – C 3	110.4(1)	111.3	110.8	111.1	111.6
C 5 – C 4 – C 7	113.2(1)	111.0	111.1	111.5	110.7
C 3 – C 4 – C 7	108.8(1)	112.0	111.7	110.1	110.7
C 6 – C 5 – C 16	124.6(2)	124.9	124.4	123.8	121.4
C 6 – C 5 – C 4	119.1(2)	120.6	121.3	121.6	122.7
C 16 – C 5 – C 4	116.1(1)	114.4	114.3	114.5	115.9
C 5 – C 6 – N 1	118.2(2)	118.2	118.7	120.0	120.0
C 5 – C 6 – C 20	129.6(2)	128.0	128.0	122.7	124.5
N 1 – C 6 – C 20	112.3(2)	113.8	113.3	117.3	115.5
C 8 – C 7 – C 4	119.2(2)	119.5	120.0	118.6	118.9
C 12 – C 7 – C 4	121.4(2)	121.3	121.1	121.5	121.2
O 1 – C 9 – C 8	122.1(2)	116.7	116.8	116.4	116.0
O 1 – C 9 – C 10	117.7(2)	122.4	122.3	122.5	123.0
O 2 – C 13 – O 3	123.2(2)	120.8	121.1	117.3	120.0
O 2 – C 13 – C 3	121.6(2)	127.9	126.2	127.0	127.8
O 3 – C 13 – C 3	115.2(1)	111.3	112.7	115.7	112.2
C 13 – O 3 – C 14	118.5(1)	117.7	121.0	117.5	119.7
C 15 – C 14 – O 3	110.0(2)	110.8	110.8	111.1	112.5
O 4 – C 16 – O 5	122.4(2)	120.9	120.6	117.5	120.0
O 4 – C 16 – C 5	122.1(2)	123.9	123.4	127.4	127.8
O 5 – C 16 – C 5	115.5(2)	115.2	116.0	115.1	112.2
C 16 – O 5 – C 17	117.7(2)	116.7	120.0	117.5	119.7
O 5 – C 17 – C 18	106.4(2)	111.0	111.0	111.1	112.5

Table 6. UV-Vis spectral data for diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (I) and 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (II).

Compound	Experimental λ_{max} [nm]	B3LYP (6-31G) λ_{max} singlet [nm]	B3LYP (6-31G) λ_{max} 50-50 [nm]	HF (6-31G) λ_{max} singlet [nm]	HF (6-31G) λ_{max} 50-50 [nm]
I	220, 272, 320, 374	286, 351, 353	320, 351, 353	204, 205, 253	253, 272, 275
II	220, 274, 320, 376	295, 337, 351	337, 351	202, 204, 254	254, 256, 270

Table 7. IR spectral data for diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (I) and 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (II).

Com-pound	Functional group	Experimental $\bar{\nu}$ [cm^{-1}]	B3LYP (6-31G) $\bar{\nu}$ [cm^{-1}]	B3LYP (6-31G) $\bar{\nu}$ [cm^{-1}] scaled	HF (6-31G) $\bar{\nu}$ [cm^{-1}]	HF (6-31G) $\bar{\nu}$ [cm^{-1}] scaled	AM1 $\bar{\nu}$ [cm^{-1}]	AM1 $\bar{\nu}$ [cm^{-1}] Scaled	PM3 $\bar{\nu}$ [cm^{-1}]	PM3 $\bar{\nu}$ [cm^{-1}] scaled
I	ν O–H	3308	3667	3594	4047	3723	3461	3299	3889	3796
	ν N–H	3352	3651	3578	3914	3601	3466	3304	3376	3295
	ν C=O		1663	1630	1829	1683	2059	1963	1976	1929
	ν C=O	1650	1662	1629	1828	1682	2046	1950	1968	1921
	ν C=C		1708	1674	1876	1726	1851	1764	1884	1839
	ν C=C		1694	1660	1853	1705	1821	1736	1856	1812
	ν C=C		1673	1640	1822	1676	1788	1704	1801	1758
	ν C=C	1595	1650	1617	1794	1650	1784	1701	1783	1740
	ν C=C	1473	1567	1536	1698	1562	1680	1601	1633	1594
II	ν O–H		3665	3592	4049	3725	3463	3301	3890	3797
	ν N–H	3347	3642	3569	3913	3600	3466	3304	3375	3294
	ν C=O	1662	1660	1627	1825	1679	2061	1965	1978	1931
	ν C=O		1654	1621	1797	1653	2050	1954	1974	1927
	ν C=C		1713	1679	1870	1720	1851	1764	1884	1839
	ν C=C		1697	1663	1856	1708	1821	1736	1853	1809
	ν C=C		1674	1641	1821	1675	1794	1710	1801	1758
	ν C=C	1591	1643	1610	1789	1646	1775	1692	1786	1743
	ν C=C	1488	1543	1512	1668	1535	1663	1585	1609	1571

[1] The characteristic vibrations of O-H and N-H bonds are very close

IR (vibrational) spectra

IR spectra of the two isomeric 1,4-DHPs were calculated. The data about vibration frequencies must be scaled by a scaling factor appropriate for the different methods, because the theoretical vibrations are harmonic and the experimental ones are anharmonic. The values of the scaling factor for DFT methods is 0.98 and for HF methods – 0.92, for AM1 – 0.9532 and for PM3 – 0.9761 [23]. Some of the characteristic IR frequencies for the two compounds are compared with the calculated ones in Table 7.

Some of the vibrations obtained by calculation are not very close to the experimental ones, which is due to fact, that the molecules of the corresponding compounds have several hydrogen bonds – intra- and intermolecular, which stabilize the structure of the corresponding compounds and the calculation methods have very low capability to describe hydrogen bonding. Some differences between results obtained with semi-empirical and *ab initio* methods are due to the different type of IR vibrations calculated (the scaling factors of AM1 and PM3 try to reproduce the true fundamental frequencies; in contrast, the scaling factors for DFT B3LYP and HF try to reproduce the zero point energies).

Calculation of other physicochemical properties

Some other physicochemical constants for I and II, as dipole moments and energy of HOMO and LUMO, calculated by the quantum mechanical (*ab initio* and semi-empirical) methods, are given in Table 8.

From the calculated physicochemical parameters it can be seen that these two isomeric 1,4-DHPs are comparatively polar compounds. *Ab initio* calculations (DFT and HF) showed that I is more polar than II. In contrast, semi-empirical calculations (AM1 and PM3) showed that II is more polar than I. Because of their higher precision and accuracy, *ab initio* calculations can be qualified

Table 8. HOMO and LUMO energies [eV] and dipole moments (μ) [D] of diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (I) and 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (II).

Compound		B3LYP (6-31G)	HF (6-31G)	AM1	PM3
I	HOMO	- 0.203	- 0.291	- 0.319	- 0.321
	LUMO	- 0.051	0.092	- 0.011	- 0.001
	Dipole moment	5.30	6.15	5.54	3.13
II	HOMO	- 0.205	- 0.300	- 0.319	- 0.320
	LUMO	- 0.052	0.091	- 0.011	0.000
	Dipole moment	4.48	5.18	6.58	3.15

as more reliable than semi-empirical methods. The comparatively lower values of HOMO energy, negative values of LUMO energy and HOMO/LUMO gaps for I and II mean that they are good reductors, which is in very good correlation with experimental data. The reduction properties and light sensibility of 1,4-DHPs are due to double bonds in their DHP ring.

CONCLUSIONS

Two isomeric 1,4-DHPs, known in literature, with hydroxyphenyl ring at fourth position in the DHP ring were synthesized by two different experimental procedures. The products were characterized by different physicochemical methods of analysis – melting point elemental analysis, IR, UV-Vis and X-Ray single crystal diffractometry. The molecular geometry of these compounds was optimized using the hybrid DFT method B3LYP and HF method both with 6-31G basis set and semi-empirical methods – AM1 and PM3 for comparison. The methods gave good results, comparable with the experimental data and with the literature data for similar compounds.

The same methods were used for predicting the UV-Vis and IR properties of the compounds. The comparison with the experimental data showed that the use of scaling factors of 0.98, 0.92, 0.9532 and 0.9761 for DFT, HF, AM1 and PM3, respectively, is not suitable for all predicted frequencies in the IR spectra, but is appropriate for simulation of UV-Vis spectra. The calculated other physicochemical properties of the compounds can be used in additional QSAR analysis.

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СИНТЕЗ, КРИСТАЛНА СТРУКТУРА И ТЕОРЕТИЧНО ИЗСЛЕДВАНЕ НА ДВЕ ИЗОМЕРНИ ПОЛИЗАМЕСТЕНИ ПРОИЗВОДНИ НА 1,4-ДИХИДРОПИРИДИН

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(Резюме)

1,4-Дихидропиридините са добре известни блокери на калциевите канали с широко приложение като антихипертензивни агенти. Те имат интересни спектрални и химични свойства, които са изучени експериментално и теоретично. Два изомерни полизаместени 1,4-дихидропиридини са синтезирани по три различни едностадийни схеми. Веществата диетил 4-(4-хидроксифенил)-2,6-диметил-1,4-дихидроксипиридин-3,5-дикарбоксилат (**I**) and diethyl 4-(3- хидроксифенил)-2,6- диметил -1,4- дихидроксипиридин -3,5-дикарбоксилат (**II**) са охарактеризирани с т.т., елементен анализ, ИЧ- и УВ-спектроскопия, а структурата им е доказана чрез монокристален рентгеноструктурен анализ. Съединение (I) кристализира в моноклинна кристална система и пространствена група $P2_1/c$, с параметри на елементарната клетка a = 739.1(1), b = 2769.5(3), c = 880.9(1) Å, α = 104.24(2) º, $\beta = \gamma$ = 90º, Z = 4, V = 1.7476(4) Å ^{3}. Съединение (II) кристализира в триклинна кристална система и пространствена група $P\bar{1}$, с параметри на елементарната клетка a = 742.8(1), b = 894.2(2), c = 1407.5(2) Å, α = 80.23(2) º, β = 86.86(2)^0, γ = 68.71(2)º, Z = 2, V = 0.8584(3) Å ^{3}. Спектралното поведение на оптимизираните структури е изучено с хибриден DFT метод, B3LYP and HF методи, последните два с 6-31G базисна мрежа и някои полуемпирични методи за сравнение. Теоретичните спектри са сравнени с експерименталните.