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## Synthesis and theoretical investigation of some new 4-substituted flavylum salts

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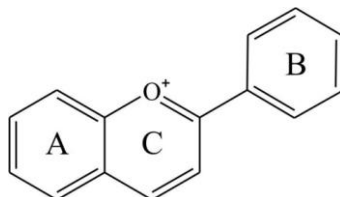
**Abstract:** Flavylum salts substituted at 4-position with bulky hydroxyphenyl substituents were synthesized by acidic condensation according to a slightly modified procedure described by Robinson and Walker. Their thermodynamic properties and conformational analysis have been studied at DFT level.

**Keywords:** 4-substituted flavylum salts, chalcones, food colorants, synthetic dyes, DFT, conformational analysis

### 1. Introduction

Anthocyanins, one important subgroup of flavonoids, are the ubiquitous pigments of many plants, especially flowers and fruits<sup>1</sup>, possessing interesting chromatic features – wide range of colors, from orange and red through purple and blue hues. They are obtained from grapes, berries, red cabbage, apples, radishes, tulips, roses and orchids, amongst others<sup>2</sup>. Anthocyanins naturally occur as glycosides of the anthocyanidins. The chromophoric aglycones (anthocyanidins) are red polyhydroxylated flavylum salts and their basic skeleton consists of an aromatic ring [A] annelated to the oxygen containing heterocyclic ring [C], which is also bonded to a third aromatic ring [B] by a carbon-carbon bond<sup>3</sup> (Fig. 1). A great diversity of anthocyanins widespread in nature are mutually differ in number of hydroxyl groups attached to

the B ring and their degree of methylation, as well as glycosyl moieties linked at different position of ring C or A, which may be acylated with the aliphatic or aromatic acids<sup>4</sup>.



**Fig. 1.** The flavylum skeleton

Anthocyanins are beneficial compounds of the human diet and its applications as prospective food colorants or reputed bioactive molecules have been exploited by food, pharmaceutical and cosmetic industries. Significant properties of these compounds, like antioxidative, anti-inflammatory and radical-scavenging activity, play vital role in the prevention of neuronal and cardiovascular diseases, cancer, diabetes, and other stress-related and chronic diseases<sup>5</sup>.

Synthetic flavylum salts possess the same basic structure as anthocyanins. Their color and physical-chemical properties have been largely investigated and are notably dependent on the nature and position of the functional groups attached to the skeleton<sup>6</sup>. It is known that influence of position C-4 is very dominant in the stabilization of these molecules<sup>7</sup> and the presence of substituent at that position is highly desirable for a food colorant because it would be stable over a wide range of pH values<sup>8</sup>.

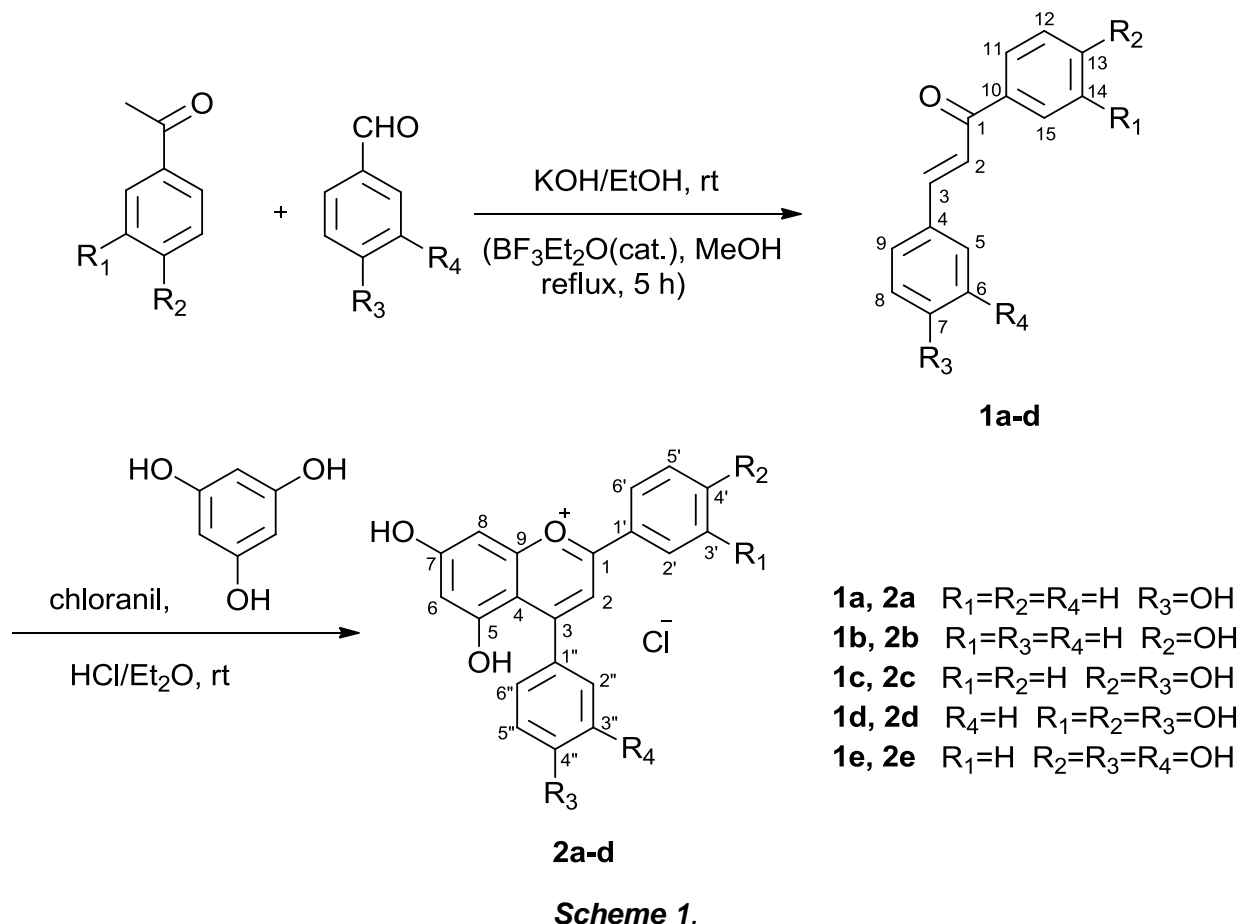
In this work, we have performed the synthesis of some 4-substituted flavylum salts through acidic condensation, and carried out their thermodynamic and conformational studies with theoretical calculation using DFT method<sup>9</sup>.

## **2. Results and discussion**

### **2.1. Synthesis**

Flavylum salts substituted in position C-4 of heterocyclic ring C are scarce<sup>10</sup>. Introduction of additional hydroxyphenylic group can lead to extended conjugation that might have deep effects in the color. It could shift the absorption maxima and thus darker and stronger nuances could be obtained<sup>11</sup>. 4-Substituted flavylum salts **2a–e** were synthesized in accordance with a slightly modified procedure described by Robinson and Walker<sup>12</sup> involving the condensation of phloroglucinol with the corresponding chalcones **1a–e** in acid solution and in the presence of chloranil as an oxidizing agent. Chalcones used in this reaction were prepared by acid- or base-catalyzed condensation from the appropriate substituted

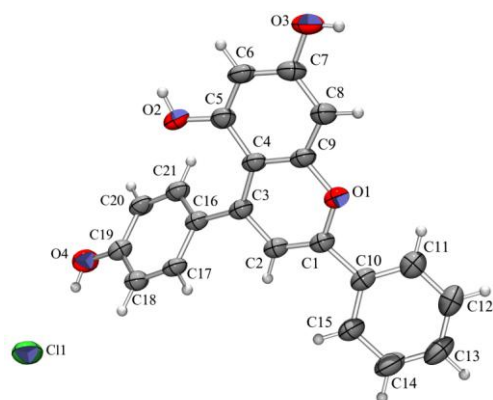
acetophenones and benzaldehydes (Scheme1). The structures of all synthesized compounds were established by spectroscopic means.



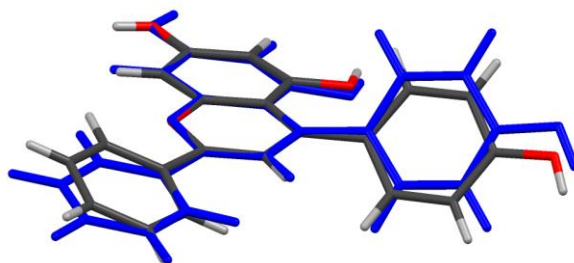
- 1a, 2a**  $R_1=R_2=R_4=H$   $R_3=OH$   
**1b, 2b**  $R_1=R_3=R_4=H$   $R_2=OH$   
**1c, 2c**  $R_1=R_2=H$   $R_2=R_3=OH$   
**1d, 2d**  $R_4=H$   $R_1=R_2=R_3=OH$   
**1e, 2e**  $R_1=H$   $R_2=R_3=R_4=OH$

## 2.2. Crystal structure

The structure of **2a** was additionally confirmed by X-ray diffraction study. Conformation of the molecule **2a** in the solid state (Fig. 2) somewhat differs from the calculated energy minimum (Fig. 3) due to its environment. Intermolecular interactions, including hydrogen bonds (Table 1) and  $\pi$ -interactions, stabilize the observed conformer. The most obvious discrepancy is the different orientation of O3 hydroxy group (Fig. 2) in the crystal it is directed towards the closest proton acceptor, the ethanol molecule. The entire hydroxyphenilic moiety is rotated to enable hydrogen bonding between O4 hydroxy group and the chlorine anion. However, due to a different orientation of the phenyl group, there is no intramolecular hydrogen bond C11-H11...O1, which is observed in the calculated structure. This is probably a result of steric hindrance in crystal packing which accommodates formation of stronger intermolecular interactions.

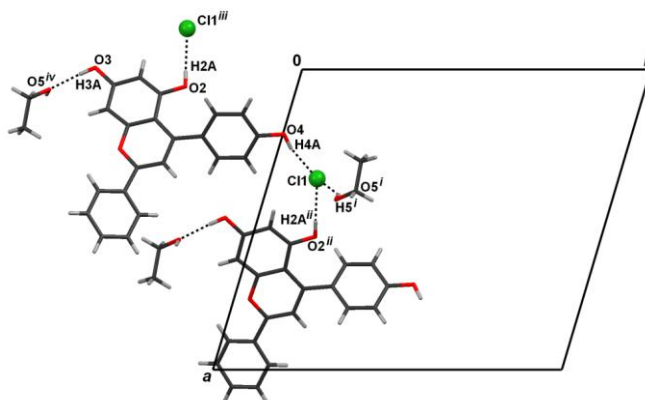


**Fig. 2.** ORTEP-3 drawing of **2a** with atom numbering scheme. Displacement ellipsoids are drawn for the probability of 50 % and hydrogen atoms are shown as spheres of arbitrary radii.



**Fig. 3.** Overlay of the experimentally determined (black) and calculated structure (blue).

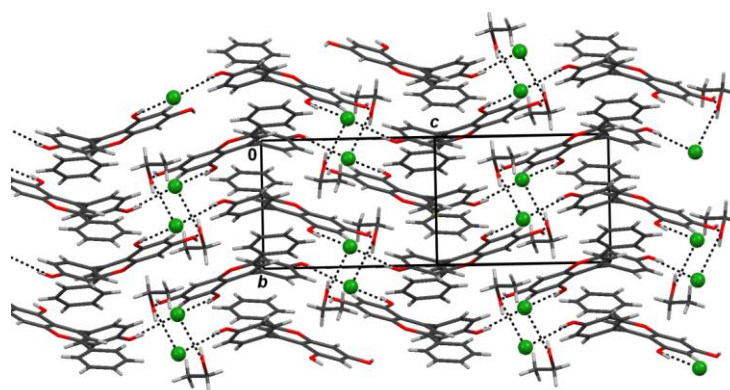
There are four proton donors in the asymmetric unit (three hydroxy groups on the molecule of **2a** and the ethanol molecule) and therefore four symmetry-independent medium-strong hydrogen bonds (Fig. 4). Also, five weak C-H...O and C-H...Cl hydrogen bonds are present (Table 1). They form hydrogen-bonded layers parallel to the plane (10-1) (Fig. 5) which are further stabilized by  $\pi$ -stacking of aromatic moieties (Table 2). 3D packing is achieved through linking the sheets by the C13-H13...O4 hydrogen bond (Table 1).



**Fig. 4.** Hydrogen bonding scheme in **2a**.

**Table 1.** Geometric parameters of hydrogen bonds.

	D–H / Å	H...A / Å	D...A / Å	D–H...A / °	Symm. op. on A
O2–H2A...Cl1	0.82	2.31	3.115(3)	170	$-1/2+x, 1/2-y, -1/2+z$
O3–H3A...O5	0.82	1.82	2.595(5)	158	$1/2-x, -1/2+y, -1/2-z$
O4–H4A...Cl1	0.82	2.34	3.134(3)	164	$x, y, z$
O5–H5...Cl1	0.82	2.40	3.095(4)	143	$x, 1+y, -z$
C2–H2...O2	0.93	2.54	3.377(4)	151	$1/2-x, -1/2+y, -1/2-z$
C6–H6...Cl1	0.93	2.81	3.567(4)	139	$-1/2+x, 1/2-y, -1/2+z$
C13–H13...O4	0.93	2.54	3.445(6)	165	$1/2+x, -1/2-y, -1/2+z$
C17–H17...O3	0.93	2.57	3.301(4)	136	$1/2+x, 1/2-y, 1/2+z$
C21–H21...O2	0.93	2.46	2.793(4)	101	$x, y, z$

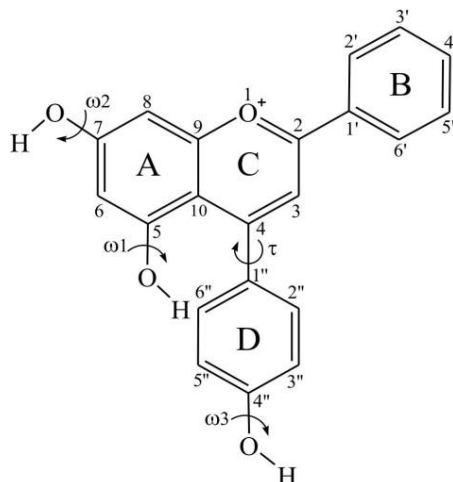
**Fig. 5.** 2D hydrogen bonded network in **2a** is parallel to the plane (10-1).**Table 2.** Geometric parameters of the  $\pi \cdots \pi$  interactions.

$\pi \cdots \pi$	Cg <sup>a</sup> ...Cg/Å	$\alpha^b$	$\beta^c$	Cg...plane (Cg2)/Å	Offset/Å	Symm.op. on Cg2
O1→C9...C16→C21	3.8641(18)	5.45(15)	29.12	3.3319(12)	1.88 <sup>d</sup>	$1/2-x, -1/2+y, -1/2-z$
O1→C9...C16→C21	3.6035(18)	5.45(15)	15.23	3.3921(12)	0.95 <sup>d</sup>	$1/2-x, 1/2+y, -1/2-z$
C4→C9...C4→C9	3.9826(19)	0.00	32.72	3.3506(14)	2.153	$-x, -y, -1-z$
C4→C9...C16→C21	3.855(2)	5.04(16)	25.51	3.3481(14)	1.66 <sup>d</sup>	$1/2-x, 1/2+y, -1/2-z$

<sup>a</sup> Cg = centre of gravity of the aromatic ring.<sup>b</sup>  $\alpha$  = angle between planes of two interacting rings.<sup>c</sup>  $\beta$  = angle between Cg...Cg line and normal to the plane of the first interacting ring.<sup>d</sup> Offset can be calculated only for the strictly parallel rings ( $\alpha = 0.00^\circ$ ). For slightly inclined rings ( $\alpha \leq 5^\circ$ ) an approximate value is given.

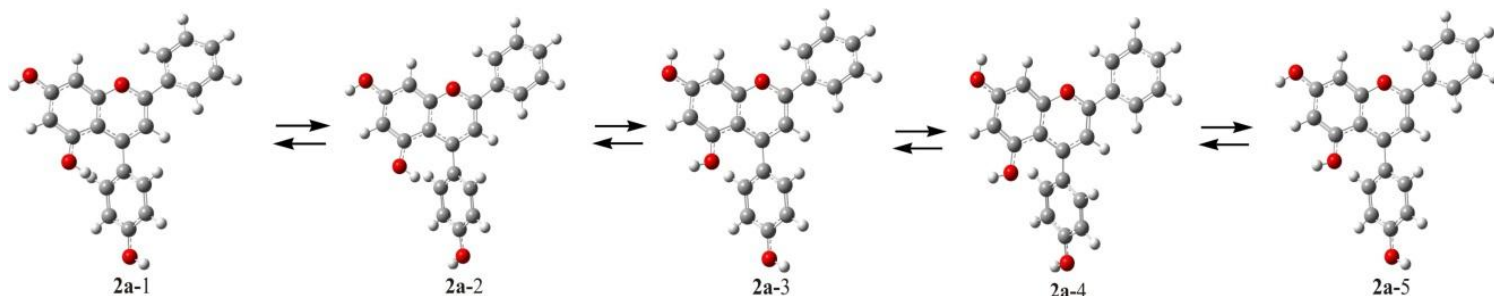
### 2.3. Structural Analysis

Potential energy surfaces are obtained in relation to the torsion angle  $\tau$  between the rings C and D, defined by the C3–C4–C1''–C2'' atoms (Fig. 6). The torsion angle  $\tau$  was scanned in steps of  $10^\circ$  without constrains on all other geometrical parameters. The effects of the rotations of hydroxyl groups related to torsion angles  $\omega_1$ (H–O5–C5–C6),  $\omega_2$ (H–O7–C7–C8), and  $\omega_3$ (H–O4''–C4''–C5'') were also studied.



**Fig. 6.** Chemical structure of flavylum cation **2a** with marked angles  $\tau$  and  $\omega_1$ - $\omega_3$ .

The rotamers of flavylum cation **2a** are presented in Figure 7, while corresponding energies are presented in Table 3. It was found that rotamers **2a-1** and **2a-2** are the most stable. Both rotamers are practically isoenergetic, because they only differ in an orientation of the OH bonds at C4''. All further calculations were done with the most stable **2a-1** rotamer as a model.



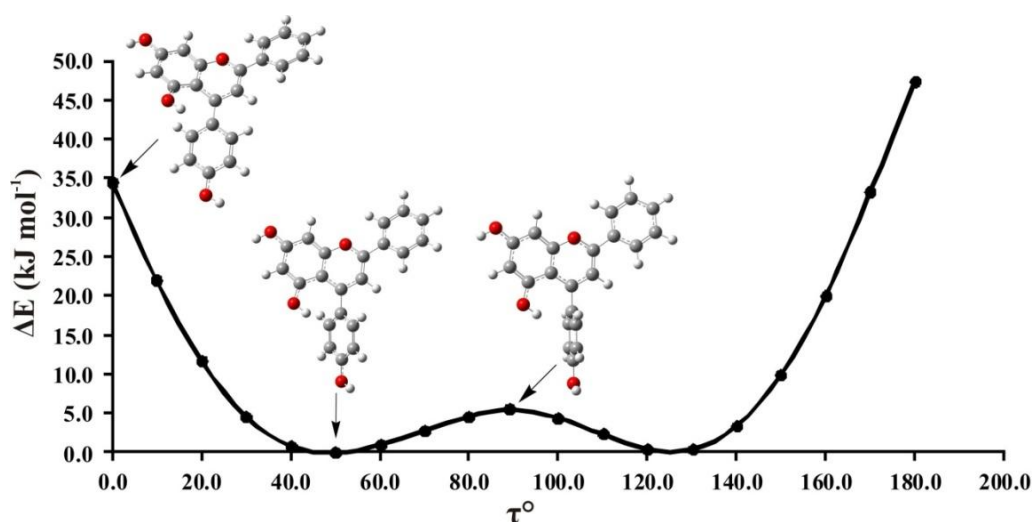
**Fig. 7.** Different rotamers of flavylum cation **2a**

**Table 3.** Relative energies ( $\text{kJ mol}^{-1}$ ) for the rotamers of **2a**.

	$\Delta E$	$\Delta H$	$\Delta G$
<b>2a-1</b>	0.00	0.00	0.00
<b>2a-2</b>	0.14	0.01	0.66
<b>2a-3</b>	2.79	2.61	4.23
<b>2a-4</b>	2.78	2.71	4.13
<b>2a-5</b>	4.91	4.84	5.84

$E$  = total energy,  $H$  = enthalpy, and  $G$  = free energy

To determine the preferred relative positions of the rings C and D, rotation around torsional angle  $\tau(\text{C3-C4-C1}''\text{-C2}'')$  of **2a-1** is performed. The obtained results are shown in Figure 8. It is obvious that there are two minima at  $50^\circ$  and  $130^\circ$ , while the local maximum of the potential energy for mutual interconversion lies at  $\tau=90^\circ$ . The low energy barrier for this interconversion (only  $5.54 \text{ kJ mol}^{-1}$ ) indicates that these two rotamers are in equilibrium. Furthermore, it could be noticed that a potential curve in intervals of  $\tau=50^\circ\text{-}0^\circ$  and  $130^\circ\text{-}180^\circ$  is very steep. The energy barrier for this rotation is much higher than in previous case ( $34.4 \text{ kJ mol}^{-1}$ ). As a consequence there is no free rotation around the  $\text{C4-C1}''$  bond and a planar structure is disabled. The main reason lies in the fact that when both rings are in the same plane there is strong steric repulsion between hydroxyl groups bonded to the  $\text{C5}$  and  $\text{H6}''$ . On the basis of these findings could be concluded that there is no full delocalization between C and D rings.



**Fig. 8.** The energy profile for rotation around  $\text{C4-C1}''$  bond of the most stable conformer of flavylium cation **2a-1**

From the results obtained by NBO analysis, in the most stable rotamer **2a-1**, the C4–C1" bond has partial double character, which is demonstrated through length of about 1.47Å and hybrid composition  $0.71(sp^{2.00})C4 + 0.70(sp^{2.19})C1''$ . The length of this bond lies between the bond lengths characteristic for aromatic and single C–C bonds, indicating weak electron delocalization between rings C and D. A slightly greater *p*-orbital contribution on C1" could be the main reason for this bond being slightly longer than a double bond.

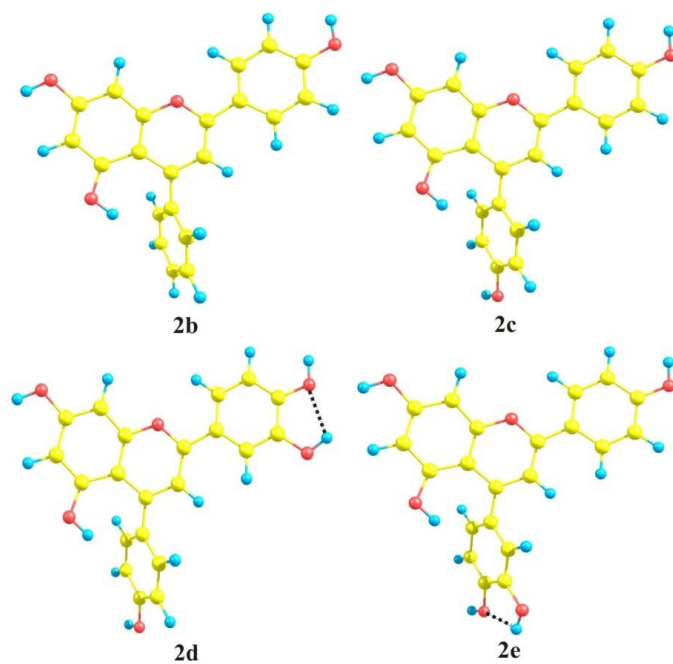
The geometrical parameters of **2a** obtained by X-ray crystallographic measurements and calculated values using M06-2X/6-311++G(d,p) model are presented in Table 4. The percentage error for bond lengths between the crystallographic data of **2a** and its calculated geometrical parameters is 0.69%. Furthermore, the correlation coefficient of 0.997, indicates the excellent agreement between experimental and theoretical values. It should be emphasized that higher percentage errors are obtained only the case of OH bonds lengths. These discrepancies may be due to the crystal packing in the lattice. It is obvious that the chosen theoretical model describes this class of compounds very well and therefore used to predict geometries of other investigated compounds (**2b-2e**) (Fig. 9).

**Table 4.** Bond lengths, bond angles and dihedral angle in neutral molecules, optimized with M06-2X method (6-311++G(d,p) basis set). Experimental values are also included.

Bond lengths (Å)	EXP	M062X	Bond angles (°)	EXP	M062X
	2a	2a-1		2a	2a-1
D(O1–C2)	1.341	1.327	A(C9–O1–C2)	120.6	123.0
D(C2–C3)	1.354	1.381	A(O1–C9–C10)	121.7	119.8
D(C3–C4)	1.410	1.398	A(O1–C2–C1')	112.3	114.1
D(C4–C10)	1.430	1.418	A(O1–C2–C3)	120.2	119.7
D(C5–C10)	1.441	1.437	A(C3–C2–C1')	127.4	126.1
D(C5–C6)	1.381	1.379	A(C2–C3–C4)	123.0	120.8
D(C6–C7)	1.390	1.401	A(C3–C4–C10)	116.8	118.8
D(C7–C8)	1.387	1.394	A(C3–C4–C1'')	115.3	117.7
D(C8–C9)	1.384	1.374	A(C10–C4–C1'')	127.9	123.4
D(C9–O1)	1.369	1.358	A(C4–C10–C5)	127.8	126.9
D(C9–C10)	1.413	1.425	A(C4–C10–C9)	117.6	117.4
D(C2–C1')	1.469	1.457	A(C9–C10–C5)	114.5	115.7
D(C1'–C2')	1.384	1.402	A(C10–C5–C6)	120.3	120.1
D(C2'–C3')	1.391	1.385	A(C10–C5–O5)	119.6	124.3
D(C3'–C4')	1.383	1.393	A(C6–C5–O5)	120.1	115.6
D(C4'–C5')	1.365	1.393	A(C5–C6–C7)	121.7	120.9
D(C5'–C6')	1.389	1.385	A(C6–C7–C8)	120.8	121.1
D(C6'–C1')	1.395	1.402	A(C6–C7–O7)	117.4	116.6



D(C4–C1'')	1.467	1.472	A(C8–C7–O7)	121.8	122.2
D(C1''–C2'')	1.408	1.407	A(C7–C8–C9)	116.9	117.4
D(C2''–C3'')	1.371	1.380	A(C8–C9–C10)	125.8	124.4
D(C3''–C4'')	1.401	1.400	A(C8–C9–O1)	112.5	115.8
D(C4''–C5'')	1.402	1.398	A(C1'–C2'–C3')	119.5	119.9
D(C5''–C6'')	1.370	1.384	A(C2'–C3'–C4')	120.4	120.1
D(C6''–C1'')	1.408	1.401	A(C3'–C4'–C5')	120.0	120.3
D(O5–C5)	1.343	1.336	A(C4'–C5'–C6')	120.7	120.0
D(O7–C7)	1.344	1.332	A(C5'–C6'–C1')	119.5	119.9
D(O4''–C4'')	1.342	1.341	A(C6'–C1'–C2')	120.0	119.8
D(H5–O5)	0.820	0.965	A(C6'–C1'–C2)	118.9	120.2
D(H7–O7)	0.820	0.963	A(C2–C1'–C2')	121.1	120.0
D(H4''–O4'')	0.820	0.963	A(C1''–C2''–C3'')	122.3	120.7
			A(C2''–C3''–C4'')	120.2	119.8
			A(C3''–C4''–C5'')	118.3	120.1
			A(C3''–C4''–O4'')	123.3	123.1
			A(C5''–C4''–O4'')	118.4	116.8
			A(C4''–C5''–C6'')	121.1	119.8
			A(C5''–C6''–C1'')	121.4	120.8
			A(C6''–C1''–C2'')	116.7	118.9
			A(C6''–C1''–C4)	124.0	120.0
			A(C2''–C1''–C4)	119.1	121.0
			$\tau$ (C3–C4–C1''–C2'')	41.36	48.55



**Fig. 9.** The optimized structures of rotamers of flavylum cations **2b-e**

### 3. Conclusion

Flavylium salts with phenyl group in position 4 and OH groups in different position in the rings B and D were synthesized in moderate yields by an easy two-step synthesis. These compounds have several potential applications, due to the remarkable chemical versatility of flavylium salts, both in the ground and excited states. On the basis of their specific chemical properties, their applications in the food industry, pharmaceutical and cosmetic industries, as well as in manufacturing of organoelectronic and photovoltaic devices could be expected.

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