



Synthesis and theoretical investigation of some new 4-substituted flavylium salts



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ABSTRACT

Flavylium salts substituted at 4-position with 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.

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1. Introduction

Desirable substitution of harmful synthetic colorants with the natural ones is attractive task which opened up an extensive and active area of investigation in recent decades (Shenoy, 1993). Carotenoids and anthocyanins are amongst the most used natural colorants in the food industry. Carotenoids, isolated mostly from vegetables, such as carrots, tomatoes and peppers are liposoluble and can be used for the coloration of processed foods ranging in shade from yellow to red. Although carotenoids have several advantages for use as food colorants, such as natural connotation and good stability in the pH range of most food products, these compounds also suffer from the significant disadvantages – susceptibility to oxidative degradation and limited color range (Rodríguez-Amaya, 2015).

Anthocyanins, one important subgroup of flavonoids, are the ubiquitous pigments of many plants, especially flowers and fruits. They are obtained from grapes, berries, red cabbage, apples,

radishes, tulips, roses and orchids, amongst others. As opposed to carotenoids, anthocyanins are soluble in aqueous media, which makes them interesting for its use as natural water-soluble colorants (Jackman, Yada, Tung, & Speers, 1987; Pazmiño-Durán, Mónica Giusti, Wrolstad, & Glória, 2001). They also possess interesting chromatic features – wide range of colors, from orange and red through purple and blue hues.

Attending to their chemical nature, anthocyanins naturally occur as glycosides of the anthocyanidins. The chromophoric aglycones (anthocyanidins) are red polyhydroxylated flavylium salts and their basic skeleton (Fig. 1a) 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 (Brouillard, 1982, chap. 1).

A great diversity of anthocyanins is widespread in nature. They 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 (Kong, Chia, Goh, Chia, & Brouillard, 2003).

Anthocyanins have characteristic physical-chemical properties that impart them its unique color and stability. Because of their

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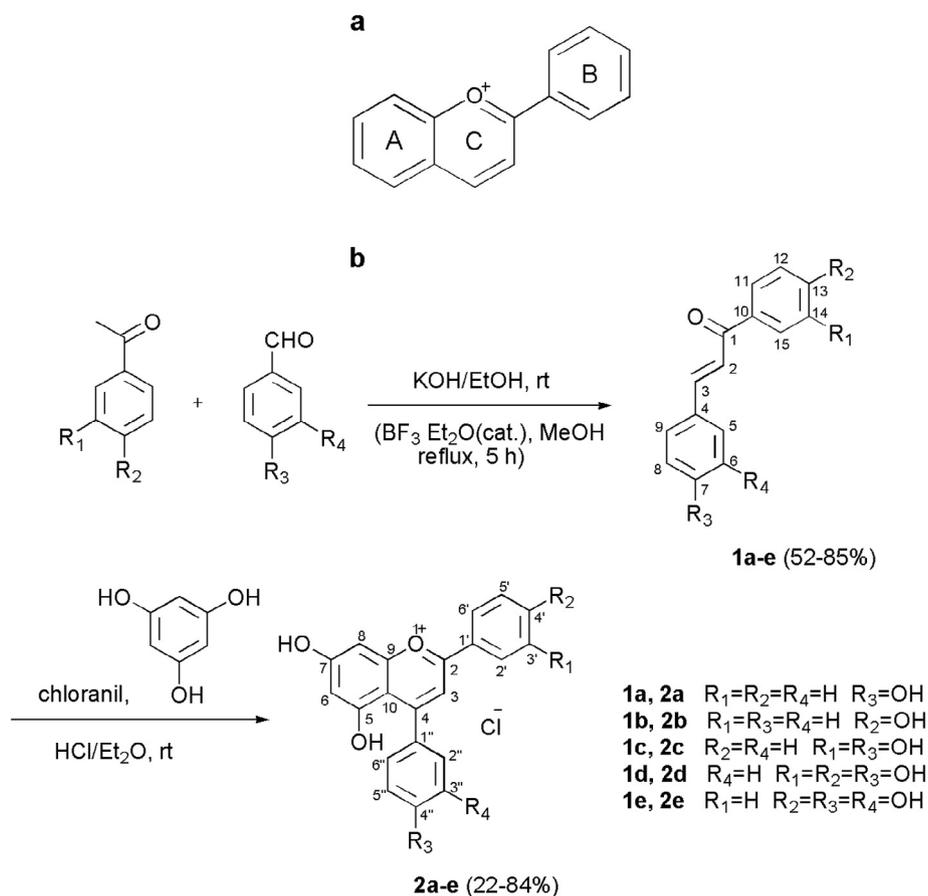


Fig. 1. General structure of the flavylium skeleton (a); Synthesis of 4-substituted flavylium salts (b).

highly reactive nature these molecules are sensitive to degradation reactions. The main factors that may affect anthocyanin chemistry and, hence, their stability and color are oxygen, temperature, light, enzymes and pH. In aqueous solution, they co-exist in pH-dependent equilibrium between at least five species (flavylium cation, carbinol base, chalcone, quinonoidal base and anionic quinonoidal base) (Castañeda-Ovando, de Pacheco-Hernández, Páez-Hernández, Rodríguez, & Galán-Vidal, 2009). This fact is crucial and firmly related to the color displayed by anthocyanins (Brouillard & Dubois, 1977). The variation and stabilization of anthocyanins have been explained by molecular stacking phenomena (Trouillas et al., 2016). Acylation with various organic acids, copigmentation, self-association and/or metal chelation may contribute pigment stabilization (Moncada et al., 2003).

Anthocyanins are also 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 (Cody, Middleton, & Harborne, 1986; Glover & Martin, 2012; Song et al., 2012; Vu et al., 2012; Youdim, Shukitt-Hale, MacKinnon, Kalt, & Joseph, 2000).

Synthetic flavylium salts possess the same basic structure as anthocyanins and study of their chemistry and photochemistry is extensive in recent years (Pina, Melo, Laia, Parola, & Lima, 2012). 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 (Pina, Petrov, & Laia, 2012). It is known that influence of position C-4 is very dom-

inant in the stabilization of these molecules (García-Viguera, & Bridle, 1999; Sweeny & Iacobucci, 1983) 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 (Timberlake, 1968).

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

2. Experimental

2.1. Chemicals and instrumentations

All solvents and reagents were obtained from commercial suppliers and used as received. Thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F254 plates visualized under UV radiation (254 nm) or with 50% (v/v) aqueous sulfuric acid. Flash column chromatography was carried out on Merck silica-gel 60, particle size 0.040–0.063 mm, using *n*-hexane, diethyl ether and methanol as eluents under gradient conditions. IR measurements (ATR-attenuated total reflectance) were carried out using a Thermo Nicolet FTIR instrument model 6700. 1H and ^{13}C NMR spectra were acquired on VARIAN GEMINI-2000 spectrometer operating at 200 MHz and on Bruker AVANCE III 400 spectrometer operating at 400 MHz. All NMR spectra were recorded at room temperature in DMSO- d_6 with tetramethylsilane (TMS) as an internal standard. Melting points were performed on a Mel-Temp capillary melting points apparatus, model 1001 and are uncorrected. The elemental analyses were performed by standard micro-methods using an Ele-

mental Vario ELIII CHNSO analyzer. Single crystal measurement was performed on an Oxford Diffraction Xcalibur Nova R (microfocus Cu tube) at room temperature.

2.2. Synthesis

2.2.1. (E)-3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one (1a)

4-Hydroxybenzaldehyde (5 g, 41 mmol) and acetophenone (4.93 g, 41 mmol) were added to the 50% KOH solution in 96% ethanol (40 ml) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then poured into cold HCl solution (300 ml, 0.5 M). The resulting solution was extracted with diethyl ether (3 × 50 ml), the combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Recrystallization from ethanol afforded yellow crystals of **1a** (7.82 g) in 85% yield with sufficient purity for spectral analysis, as revealed by GC.

2.2.2. The general procedure for the synthesis of chalcones **1b–e**

To a stirred solution of appropriate acetophenone (13 mmol) and benzaldehyde (13 mmol) in 15 ml of methanol, a catalytic amount of BF₃·Et₂O (10 drops) was added at room temperature. After addition of the catalyst, the reaction mixture was refluxed for 5 h and then cooled to room temperature. After addition of 100 ml of ether, the resulting solution was washed with water (3 × 50 ml) to remove BF₃ complexes, dried over anhydrous Na₂SO₄ and filtered. After evaporation of the solvent, a crude product was further purified by dry-flash chromatography to afford the desired chalcones **1b–e** of sufficient purity for next reaction, as revealed by TLC.

2.2.3. The general procedure for the synthesis of chromenylium salts **2a–e**

Equimolar amounts of the corresponding chalcone, phloroglucinol and chloranil were added to the stirred solution of hydrogen chloride in diethyl ether (50 ml) prepared by the method described by Matuszak and Matuszak (1967), and the resulting reaction mixture was stirred at room temperature overnight. The solid was then filtered off, washed with cold ether and recrystallized from ethanol to afford desired chromenylium salts **2a–e**. Spectral data are given in Supporting Information.

2.3. Computational methodology

Geometry optimization and frequency calculations of the conformers were performed by density functional theory (DFT), using a global-hybrid *meta*-GGA (M06-2X) functional with 54% HF (Hartree-Fock) exchange (Zhao & Truhlar, 2008a) in combination with the 6-311++G(d,p) basis set, as implemented in the Gaussian 09 package (Frisch et al., 2009). This functional also yields satisfactory overall performance for the main group thermochemistry, thermochemical kinetics and non-covalent interactions, however it cannot be used for cases where multi-reference species are or might be involved, such as transition metal thermochemistry and organometallic (Galano et al., 2016; Zhao & Truhlar, 2008b). The NBO analysis was performed by using the NBO 5.9 software (Carpenter & Weinhold, 1988; Reed & Weinhold, 1983).

Conformation analysis was performed to obtain potential energy surfaces related to the torsion angle τ between the rings C and D. The obtained structure of conformers were verified by normal mode analysis to be minimum on the potential energy surface. No imaginary frequencies were obtained. Each potential minimum obtained on this way is fully reoptimized in gas and DMSO as a solvent. The M06-2X/6-311++G(d,p) level of the theory was employed.

The solvent effect was taken into account in geometry optimization by using the SMD model (Marenich, Cramer, & Truhlar, 2009). The gas-phase and DMSO geometries were used to predict the experimental geometry obtained from the X-ray crystal structure analysis.

3. Results and discussion

3.1. Synthesis

Flavylium salts substituted in position C-4 of heterocyclic ring C are scarce (Amić & Trinajstić, 1991; Baranac, Amić, & Vukadinovic, 1990; Chassaing, Isorez, Kueny-Stotz, & Brouillard, 2008; Chassaing, Isorez- Mahler, Kueny-Stotz, & Brouillard, 2015; Davidović-Amić, Amić, & Trinajstić, 1994; Freitas, Shimizu, Dias, & Quina, 2007; Leopoldini, Rondinelli, Russo, & Toscano, 2010; Quartarolo & Russo, 2011; Roehri-Stoeckel, Gonzalez, Fougerousse, & Brouillard, 2001). 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 (McClelland & McGall, 1982).

4-Substituted flavylium salts **2a–e** were synthesized in accordance with a slightly modified procedure described by Robinson and Walker (1934) 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. The synthetic pathways are given in Fig. 1b. The structures of the synthesized compounds were established by spectroscopic means (IR, ¹H and ¹³C NMR) and the data are given in Supporting information. The structures were also corroborated by comparison of their spectral data to those published in the literature. The salts **2a**, **2c**, **2d** and **2e** are new compounds, while **2b** was synthesized a few decades ago as a substance that could be used as color additive for fruit drinks and juices, stable on light in the presence of ascorbic acid or traces of iron (Timberlake & Bridle, 1967).

3.2. Crystal structure

The structure of **2a** was additionally confirmed by X-ray diffraction study. ORTEP representation of **2a** is shown in Fig. 2(a). Conformation of the molecule **2a** in the solid state somewhat differs from the calculated energy minimum due to its environment (Fig. 2(b)). Intermolecular interactions, including hydrogen bonds (Table S2) and π -interactions, stabilize the observed conformer. The most obvious discrepancy is the different orientation of O3 hydroxy group at position C7: in the crystal it is directed towards the closest proton acceptor, the ethanol molecule. The entire hydroxyphenylic 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.

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. 2(c)). Also, five weak C-H...O and C-H...Cl hydrogen bonds are present (Table S2). They form hydrogen-bonded layers parallel to the plane (10-1) (Fig. 2(d)) which are further stabilized by π -stacking of aromatic moieties (Table S3). 3D packing is

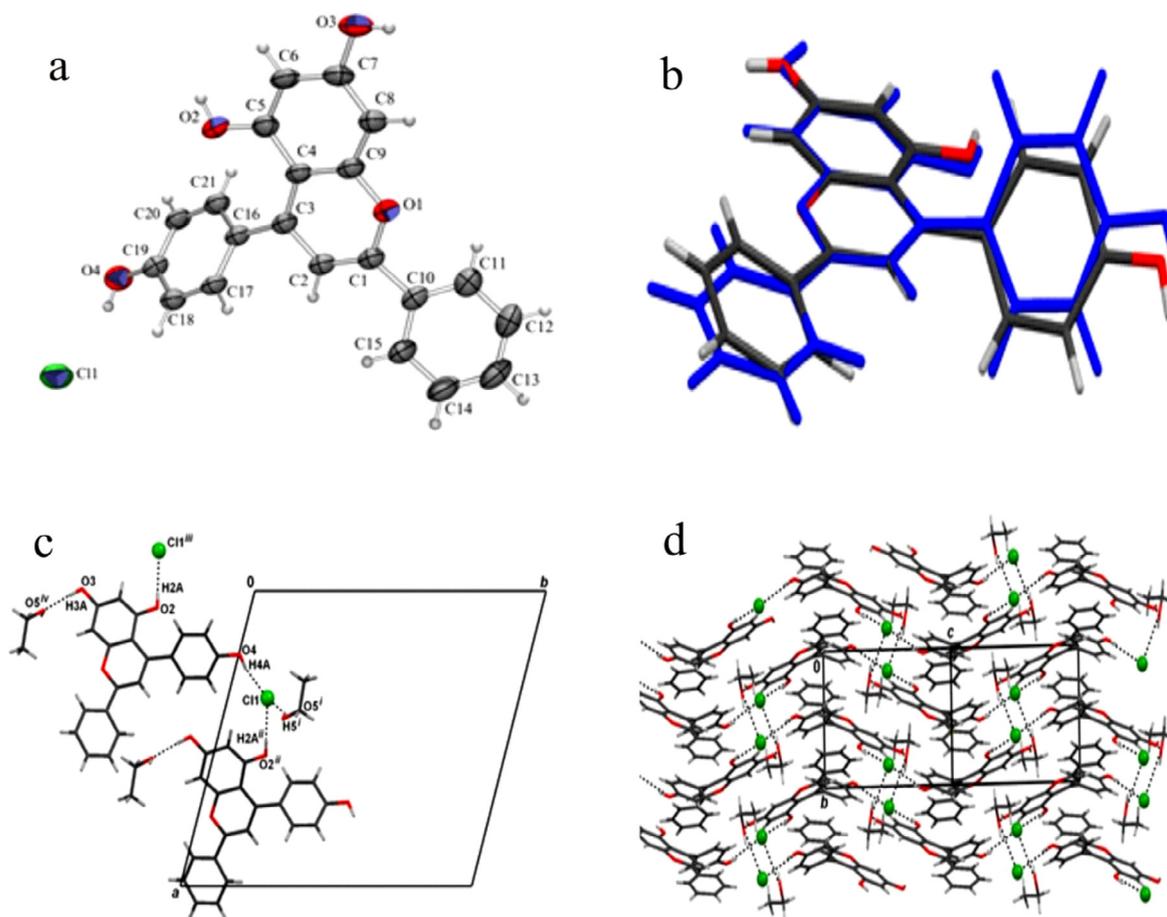


Fig. 2. ORTEP-3 drawing of 2a with atom numbering scheme. Displacement ellipsoids are drawn for the probability of 50% and hydrogen atoms are shown as spheres of arbitrary radii (a); Overlay of the experimentally determined (black) and calculated structure (blue) (b); Hydrogen bonding scheme in 2a (c); 2D hydrogen bonded network in 2a is parallel to the plane (10-1) (d). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

achieved through linking the sheets by the C13-H13...O4 hydrogen bond (Table S2).

3.3. Structural analysis

Potential energy surfaces are obtained in relation to the torsion angle τ between the rings C and D, defined by the C3–C4–C1''–C2'' atoms (Fig. 3). The torsion angle τ was scanned in steps of 10° without constraints on all other geometrical parameters. The effects of the rotations of hydroxyl groups related to torsion angles ω_1 (H–O5–C5–C6), ω_2 (H–O7–C7–C8), and ω_3 (H–O4''–C4''–C5'') were also studied.

The rotamers of flavylium cation 2a and their corresponding energies are presented in Fig. 4. 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.

To determine the preferred relative positions of the rings C and D, rotation around torsional angle τ (C3–C4–C1''–C2'') of 2a-1 is performed. The obtained results are shown in Fig. 5. It is obvious that there are two minima at 50° and 130°, 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 kJ mol⁻¹) indicates that these two rotamers are in equilibrium. Furthermore, it could be noticed that a potential curve in intervals of $\tau = 50^\circ$ –0° and 130°–180° is very steep. The energy bar-

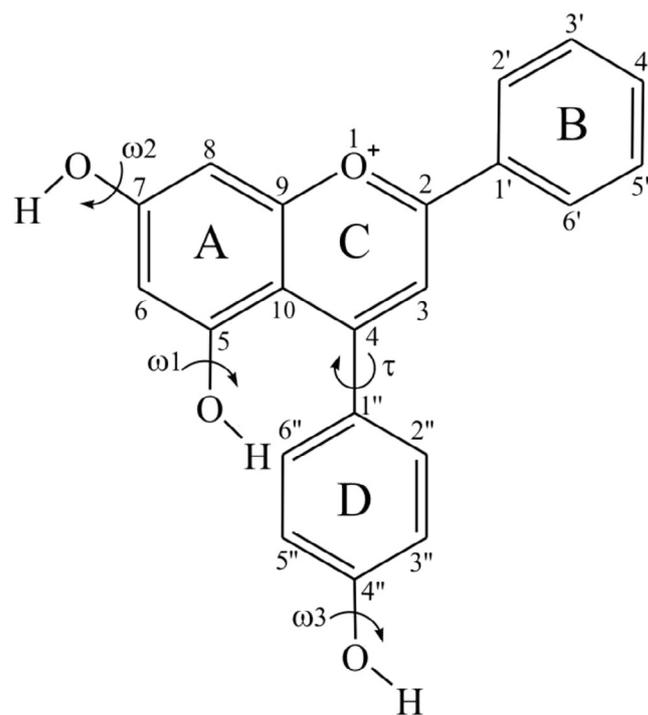


Fig. 3. Chemical structure of flavylium cation 2a with marked angles τ and ω_1 – ω_3 .

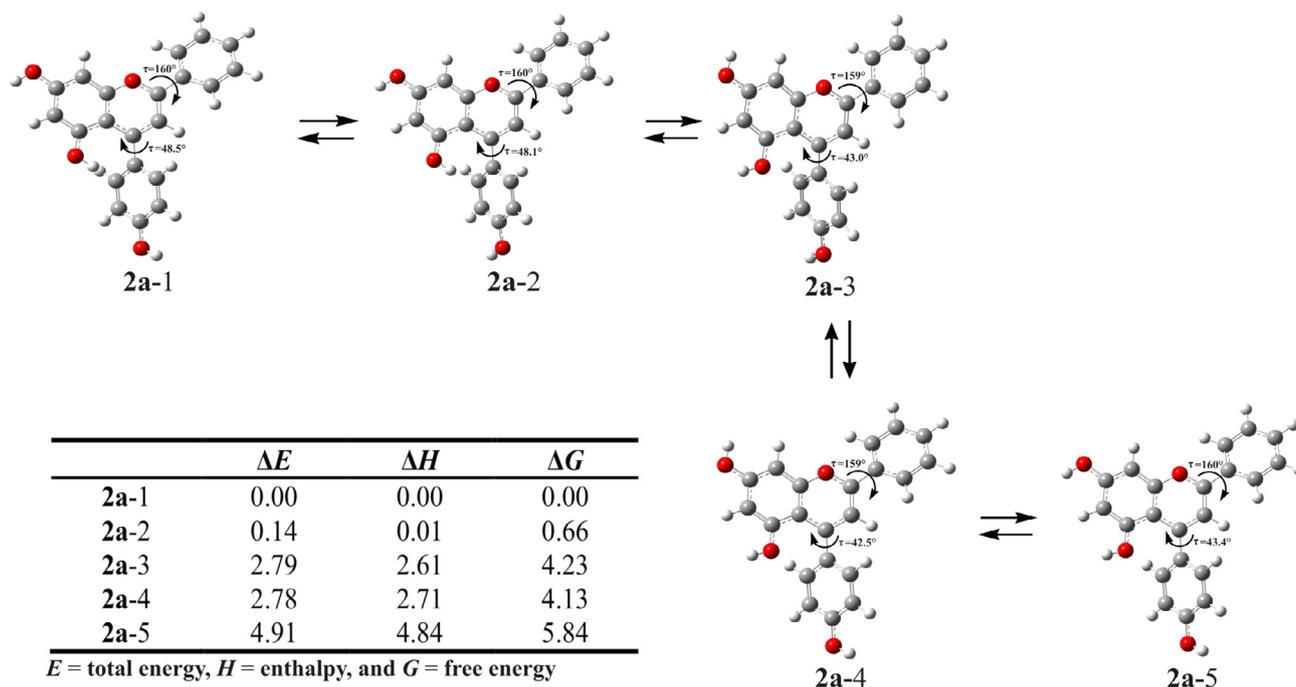


Fig. 4. Different rotamers of flavylum cation **2a** and their relative energies (kJ mol^{-1}).

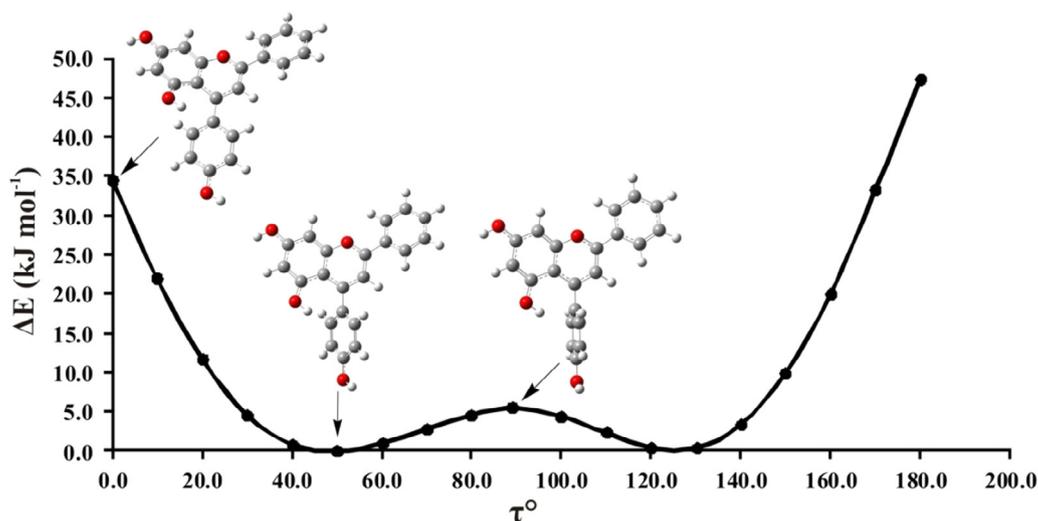


Fig. 5. The energy profile for rotation around $\text{C4-C1}'$ bond of the most stable conformer (**2a-1**) of flavylum cation.

rier for this rotation is much higher than in previous case (34.4 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 C5 and $\text{H6}''$. On the basis of these findings could be concluded that there is no full delocalization between C and D rings.

From the results obtained by NBO analysis (Table S4), in the most stable rotamer **2a-1**, the $\text{C4-C1}'$ bond has partial double character, which is demonstrated through length of about 1.47 \AA and hybrid composition $0.71(\text{sp}^{2.00})\text{C4} + 0.70(\text{sp}^{2.19})\text{C1}'$. 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 $\text{C1}'$ 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, in gas phase and DMSO, using M06-2X/6-311++G(d,p) model are presented in Tables S5 and S6. The percentage errors for bond lengths between the crystallographic data of **2a** and their calculated geometrical parameters in gas phase and DMSO are 0.69% and 0.67%, respectively. Furthermore, the correlation coefficients of 0.997 and 0.996, indicate 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. 6). Geometrical parameters for the most stable conformers of compounds **2b–2e** are presented in the Table S6.

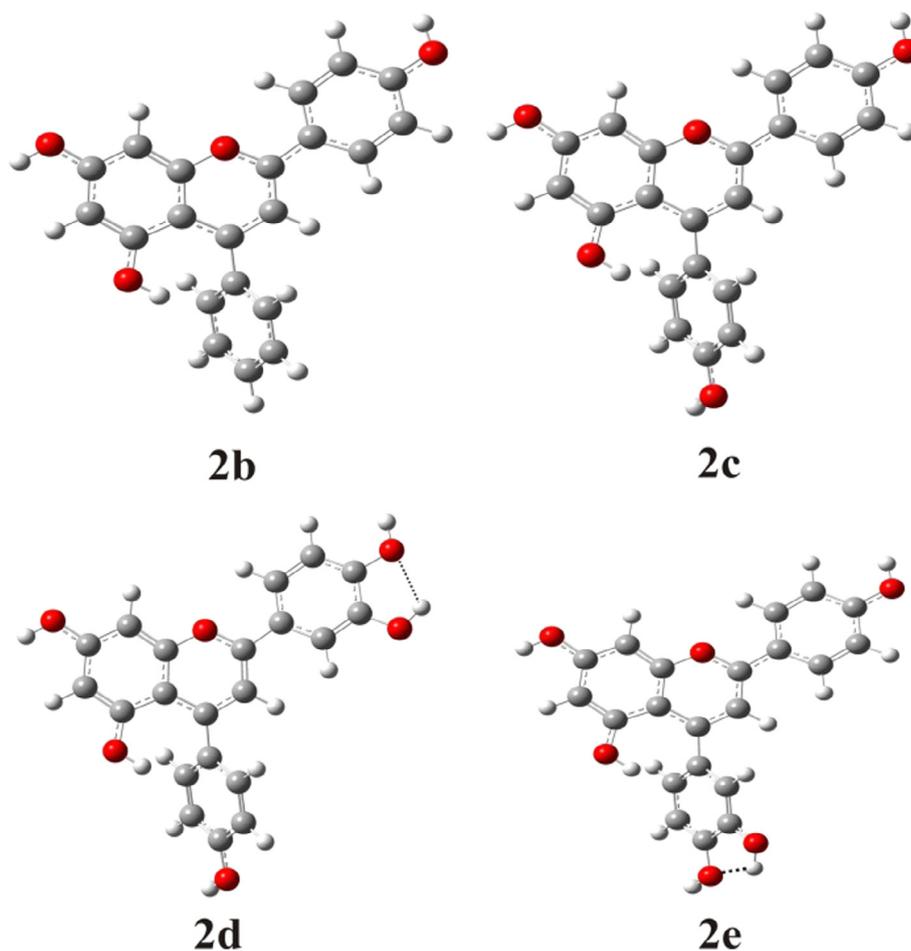


Fig. 6. The optimized structures of the most stable rotamers (2b-1–2e-1) of flavylium cations 2b-e (dotted lines represent intramolecular H-bonds).

4. Conclusion

Flavylium salts with phenyl group in position 4 and OH groups in different position in the rings B and D can be 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 can expect their applications in the food industry, pharmaceutical and cosmetic industries, as well as in manufacturing of organoelectronic and photovoltaic devices.

Conflict of interest statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.foodchem.2017.02.139>.

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