Chemistry of Heterocyclic Compounds, Vol. 50, No. 3, June, 2014 (Russian Original Vol. 50, No. 3, March, 2014)

QUANTUM-CHEMICAL ANALYSIS OF THE ALGAR–FLYNN–OYAMADA REACTION MECHANISM

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This work is devoted to improving the understanding of Algar–Flynn–Oyamada reaction mechanism and the analysis of factors that affect the formation of flavonols. The calculation of thermodynamic parameters for the key reaction steps pointed to a mechanism involving chalcone epoxides as intermediates. A correlation was identified between the nucleophilicity of oxygen atom at position 2′ of epoxide anions and the yields of flavonols. An increased charge at the nucleophilic center was shown to reduce the effectiveness of β-cyclization of epoxide anions.

Keywords: chalcone, epoxychalcone, flavonol, Algar-Flynn-Oyamada reaction, reaction mechanism.

3-Hydroxyflavones (flavonols) are a class of natural benzopyran dyes that have been of interest to physical chemistry, pharmacology, and medicine for almost a century [1-4]. A large number of biologically active flavonol derivatives have been synthesized. These compounds exhibit high antioxidant activity and are characterized by unusual spectral properties – a two-band fluorescence with high quantum yields. Approximately ten different approaches exist for the synthesis of flavonols [5-10], but the majority of publications [11, 12] report the use of the Algar–Flynn–Oyamada (AFO) reaction (Scheme 1*a*, route A). The reasons are the relative simplicity and convenience of the AFO reaction, which according to the classical methodology [13] involves the oxidation of 2'-hydroxychalcones **1** with hydrogen peroxide in alkaline alcohol solution. The conditions of the AFO reaction are easily modified within known limits by using various types of solvents, bases, and occasionally oxidants, as well as by changing the temperature of the reaction mixture. An interesting feature of this method is the change in the reaction direction when using 6'-alkoxy-2'-hydroxy-chalcones. In that case the flavonols **4** are detected in trace quantities only, while the main products are the aurones **6** (Scheme 1*a*, route B) [14].

A wide range of publications have been devoted to the study of the AFO reaction. The key stages of the process are known to be the cyclization and oxidation, while the precursors to flavonols are the flavanonols **3** [15]. However, there is still no clear consensus in the literature regarding the mechanism of this transformation. Two main hypotheses exist, the first one of which predicts the conversion of the 2'-hydroxychalcone **1** or its

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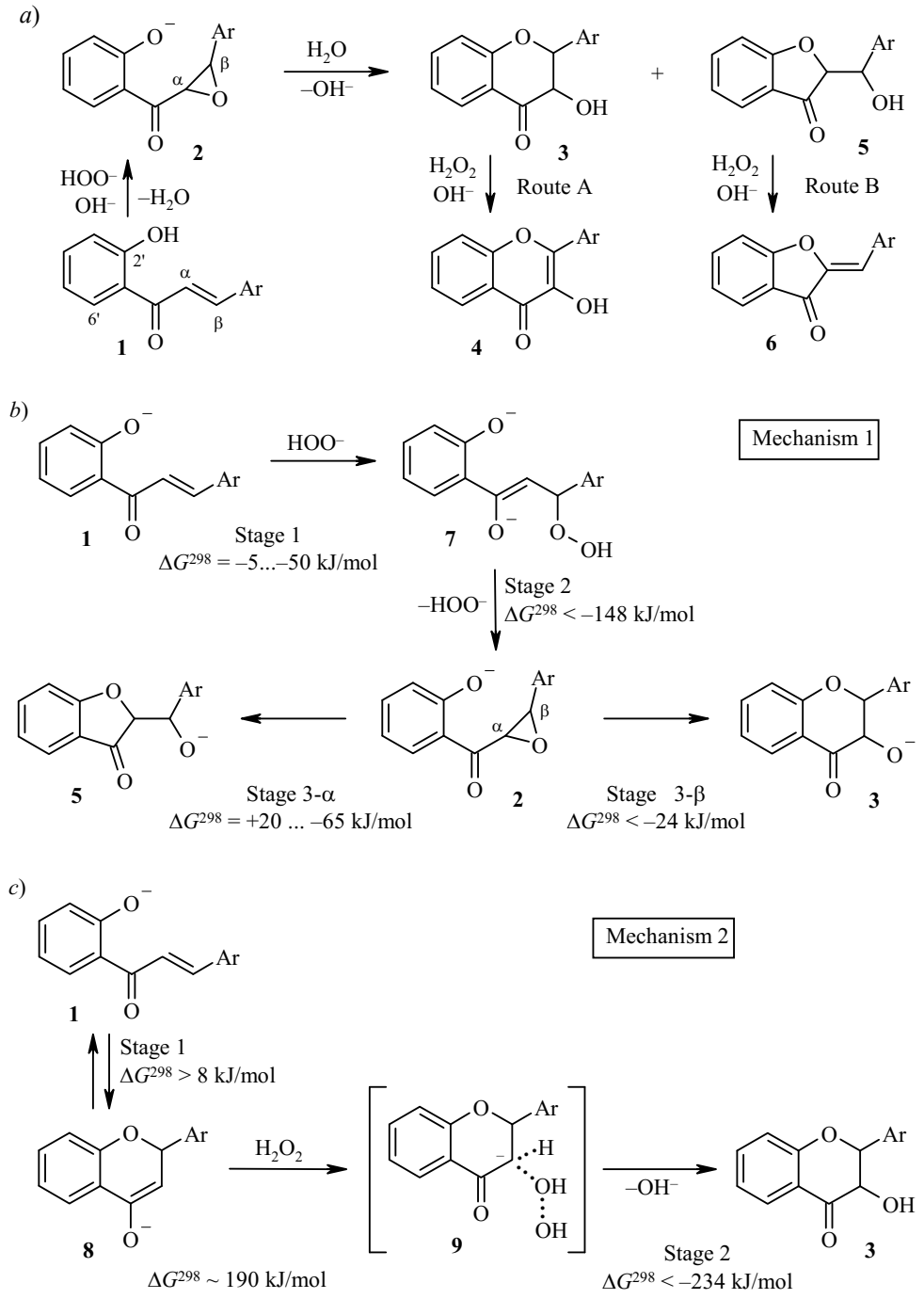
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 431-439, March, 2014. Original article submitted January 27, 2014.

anion to the chalcone epoxide **2** by the action of hydroperoxide anion (Scheme 1*a*). An intramolecular cyclization of epoxide may occur at either the β- or α-atom, resulting in the eventual formation of the flavonol **4** (route A) or the aurone **6** (route B), respectively [16]. This mechanism is supported by the successful cyclization of 2'-hydroxychalcone epoxide obtained by a different method [17].

Scheme 1



Mechanisms proposed for the AFO reaction

The proposed formation of epoxides during this reaction explains its further course. Such a mechanism was used in the work [18] to interpret the formation of aurones from the 6'-alkoxy-2'-hydroxychalcone epoxide

anions. The presence of 6'-alkoxy substituents was experimentally demonstrated to increase the base strength of the anions of the aforementioned compounds **2**. It was also assumed that a substituent at position 6' interferes with the conformation suitable for β-cyclization, and facilitates α-cyclization. The stereochemistry of benzofuran derivatives formed by AFO reaction was studied, and the published findings [19] support the described mechanism.

Nevertheless, as mentioned before, the postulated intermediate epoxides were obtained by a different route. The direct formation of the epoxides **2** in AFO reaction remain unproved. Chalcones should exist under the AFO reaction conditions as mainly deprotonated, not neutral species, therefore the formation of the epoxide **2** should be preceded by the interaction of two negatively charged particles: 2'-hydroxychalcone anion and hydroperoxide anion (Scheme 1*b*). It has been experimentally demonstrated [20] that anions of hydroxychalcones not capable of intramolecular cyclizations do not form epoxides under the AFO reaction conditions.

According to the second hypothesis, the formation of a flavonol starts with cyclization, leading to an equilibrium between the anions of 2'-hydroxychalcone **1** and the flavanone **8** [13] (Scheme 1*c*). It was established earlier that the equilibrium in solutions of α-alkoxychalcones (2-alkoxy-1,3-diaryl-2-propen-1-one derivatives) is shifted towards the cyclic product **8** [21]. As shown in the work [20], further oxidation (addition of hydroxyl group to flavanone) can not involve a radical mechanism. The flavanonol **3** is formed by electrophilic attack of hydrogen peroxide at the C-3 carbon atom of the flavanone anion **8**. A concerted process combining the two stages has also been proposed [20].

The suggested mechanisms are based on indirect experimental data, and the conclusions about these mechanisms are only preliminary. In order to identify the most likely hypothesis, we calculated the Gibbs energy values for the key stages in the aforementioned mechanisms for the flavonols **4a-l** (Scheme 2, Table 1). The availability of many compounds with substituents at the 7 and 4' atoms enable an evaluation of electronic effects in the AFO reaction. We should specifically emphasize that the given substituents can not have a steric influence on the result of the transformation.

The thermodynamic characteristics and the atomic charges were calculated with the semiempirical methods RM1 and PM6. As shown in the literature [22-25], the accuracy of the computational methods used is not inferior to DFT calculations, and the calculated results show satisfactory correlation with experimental data.

The quantum-chemical calculations were performed in two stages. At the first, preliminary stage the RM1 method was used for a sufficiently effective and quick molecular geometry optimization. The further calculations were performed with the PM6 method, including geometry refinement followed by the calculation of thermodynamic properties of the molecules, the entalphy and entropy of formation, and the corresponding Gibbs energy (ΔG^{298}). The PM6 method was selected due to the more accurate calculations of the thermodynamic parameters of the molecules [26]. The atomic charges obtained according to the RM1 and PM6 methods were not identical, but the differences were rather small and the changes were symbatic. Nevertheless, in this work we present the values of atomic charges obtained by the RM1 method, because this method is characterized by a higher accuracy of calculations with respect to the electric parameters of molecules [26].

Scheme 2

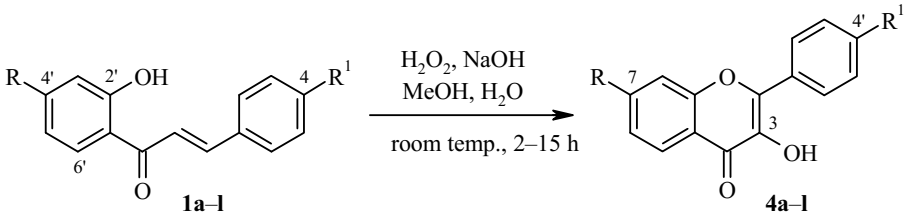


TABLE 1. Gibbs Energy Values ΔG^{298} (kJ/mol) for the Separate Stages of AFO Reaction (Calculated According to the PM6 Method for H_2O Solution at 298 K)

Compound	R	R^1	Mechanism 1				Mechanism 2	
			Stages				Stages	
			1	2	3-β	3-α	1	2
a	H	H	-31.5	-170.9	-38.2	-12.3	12.1	-238.4
b	OH	H	-5.2	-200.7	-47.2	-29.1	13.5	-264.4
c	NEt_2	H	-19.5	-181.0	-45.6	-20.4	8.9	-248.3
d	OMe	H	-44.6	-154.2	-37.9	-15.1	15.1	-237.3
e	OCH_2OMe	H	-49.5	-148.2	-35.2	-9.7	21.5	-241.9
f	OCH_2Ph	H	-42.2	-165.0	-24.8	0.3	23.4	-239.6
g	$OCH_2C_6H_4OMe$-4	H	-31.3	-166.7	-29.6	-9.0	24.7	-237.9
h	H	NMe_2	-24.2	-171.6	-43.8	-11.2	12.7	-235.9
i	H	OMe	-43.6	-163.3	-40.2	-53.0	8.1	-239.3
j	H	OCH_2Ph	-43.9	-151.1	-37.4	-65.0	17.9	-299.5
k	H	$OCH_2C_6H_4OMe$-4	-32.9	-157.8	-37.3	-48.3	25.8	-234.2
l	H	F	-32.5	-167.6	-43.6	20.2	9.0	-234.0

The first proposed mechanism was modified by taking into account the prevalence of anionic forms of the considered compounds under the AFO reaction conditions (Scheme 1*b*). The ΔG^{298} values of the main reaction stages, calculated as the difference between the Gibbs energy of products and the starting materials, are given in Table 1.

According to the calculations, the reactions of the anions of the chalcones **1a-l** with the peroxide anion were energetically favorable, even though the presence of substituents with a significant electron-donating effect increased the ΔG^{298}, hindering the delocalization of negative charge in the dianions **7a-l**. The subsequent cyclization stage forming the epoxide anions **2a-l** was significantly exothermic for all of the studied compounds. Both the α- and β-cyclization reactions had negative Gibbs energy values for practically all epoxides. Furthermore, the experimental data indicate that the formation of the flavanonol anions **3a-g** is more favorable by 18.1-25.4 kJ/mol, compared to the formation of the anions from 2-(α-hydroxymethylphenyl)benzofuranones **5a-g**, when the starting epoxide has a substituent at position 4'. In the cases when the epoxide contains an alkoxy group at position 4 (compounds **2i-k**), the α-cyclization products **5i-k** are more favored according to the calculations.

With regard to the second proposed mechanism (Scheme 1*c*), the first step of the intramolecular cyclization of the anions **1a-l** in aqueous medium is endothermic regardless of the substituent and its position (Table 1). Besides, for achieving this transformation, the chalcones must change conformation from the low-energy *S-cis* to the high-energy *S-trans* conformation. The following stage must likely involve the intermediates **9a-l**. The ΔG^{298} value for the reaction of their formation is approximately 190 kJ/mol, which is an insurmountable energy barrier under the conditions of AFO reaction, despite of the overall decrease in the Gibbs energy of the system during the second stage of forming the flavanonols **3a-l**.

The "synchronous" mechanism involves an interaction between a molecule of hydrogen peroxide and a chalcone anion in the high-energy *S-trans* conformation [20]. The probability of such particles colliding is lower than that of the more common bimolecular collisions and can not lead to a high yield of flavonols in AFO reaction.

Thus, the above described thermodynamic characteristics of intermediate reactions clearly confirm the hypothesis that the AFO reaction mechanism involves the epoxides **2** as intermediates. Therefore we considered it unnecessary to perform an in-depth quantum-chemical study of transition states and to calculate the activation barriers between the intermediate products. However, a predicted higher thermodynamic effectiveness of α-cyclization for the epoxides **2i-k** with the alkoxy groups at position 4 mismatches with experimental fact that corresponding chalcones **1i-k** do not form the aurones **5i-k** in the AFO reactions, that indicates a kinetic control instead of thermodynamic control of the reaction at this stage.

An experimental investigation of parameters that influence the cyclization product yield was previously performed mainly for 6'-alkoxy-substituted 2'-hydroxychalcones. The 6'-alkoxy substituents have strong mesomeric electron-donating properties and also create steric hindrance that affects the carbonyl fragment conformation in the molecules [18]. Therefore, based on the previous investigations, it is difficult to identify either the electronic or steric effect of the substituent as key to determining either α- or β-cyclization.

During the synthesis of flavonol derivatives with substituents at positions 7 or 4' by using the AFO reaction we noticed that the presence of a strong electron-donating substituent at position 4' of the chalcones **1c**-**e** substantially decreased the β-cyclization product yield (Table 2). When performing the reaction with the chalcone **1b**, featuring a 4'-hydroxy group that is deprotonated in alkaline medium, the expected 7-hydroxy-flavonol was not found in the reaction mixture. On the other hand, the unsubstituted flavonol **4a** and its derivatives **4h-l** with different substituents at position 4' were obtained in reproducibly high yields. The analysis of these findings led to the conclusion that there is a link between the magnitude of the mesomeric electron-donating effect of the substituent at position 7 of a flavonol and its yield in the AFO reaction.

Within the framework of the first considered mechanism (Scheme 1*b*) the stage of anion formation from the flavanonol **3** represents a nucleophilic attack by the phenolate anion oxygen atom on the β-carbon atom of the epoxide **2**. The substituent R in the epoxides **2b**-**g** may affect the rate of this process by modifying the nucleophilicity of the oxygen atom at position 2', as was shown for the example of 6'-alkoxy derivatives [18]. The calculation of charge distribution in the epoxide anions **2** confirmed that electron-donating substituents at position 4' increase the negative charge on the oxygen atom at position 2' (Table 2).

The magnitude of this charge showed a good correlation with the yields of flavonols: the smaller the charge at the oxygen atom, the lower was the β-cyclization product yield (Fig. 1, *a*). The obtained correlation can be explained by a decreased selectivity of attack with increasing nucleophilicity of the oxygen atom.

The calculations also allowed to estimate the effect of the R^1 substituent on the charge of the oxygen atom in the epoxide anions **3a-l**. The analysis of correlation between the atomic charge and flavonol yield for all investigated compounds allowed to propose that β-cyclization becomes the dominant process after decreasing the charge of the oxygen atom at 2' position to a certain value, after which the nucleophilicity of the anionic center has no additional effect on the reaction yield (Fig. 1, *b*). The reaction methodology was such that the yields not exceeding 85% may be rather explained by the product losses during the isolation from the reaction mixture, and not the effect of side reactions. The yields of compounds **4e**,**k** did not follow the

TABLE 2. Flavonol Yields in the AFO Reaction and the Calculated Charges on the O-2' Oxygen and C-β Carbon Atoms of the Respective Epoxide Anions **2a-l** (Calculated by the RM1 Method for a Solution in H_2O)

Compound	Yield, %	Atomic charges (q), $\bar{e}$	
		O-2'	C-β
4a	74	-0.597	0.043
4b	0	-0.667	0.035
4c	30 [27]	-0.615	0.021
4d	22	-0.620	0.042
4e	28	-0.607	0.043
4f	57	-0.604	0.043
4g	71	-0.599	0.043
4h	76	-0.602	0.055
4i	81	-0.592	0.022
4j	71 [28]	-0.597	0.055
4k	83	-0.603	0.031
4l	80	-0.595	0.044

general trend due to the lower and higher aqueous solubility, respectively, which affected the efficiency of isolation procedures.

It has been proposed [16] that the direction of AFO reaction depends on the charges on the carbon atoms in the α- and β-epoxy rings. The R^1 substituent in compounds **4h-l** has some effect on the charge of the β-atom of the ring, but we were unable to find a link between the calculated charges and flavonol yields.

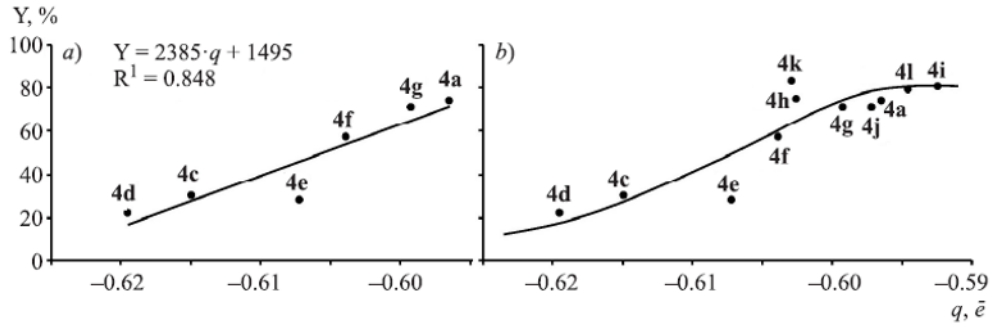


Fig. 1. The dependence of flavonol yield (Y) on the charge (*q*) of the oxygen atom at position 2' of the epoxide anions for compounds **4a-g** (*a*) and **4a-l** (*b*).

The performed investigations led to the following conclusions. The formation of the considered flavonols according to the AFO reaction involves intermediate epoxide anions, that was confirmed by the thermodynamic characteristics of the key stages in such a mechanism. When there were no substituents at position 6', the yield of flavonols was determined by kinetic control of the β-cyclization of epoxide anions through the nucleophilicity of the oxygen atom at position 2' of the epoxide anion.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 MHz) in DMSO-d_6, with TMS as internal standard. Mass spectra were recorded on a Bruker Daltonics MALDI-TOF MS instrument. Elemental analysis was performed on an Elementar Vario El Cube CHNS analyzer. The reaction progress was controlled by TLC on Merck 60 F254 plates, with visualization under UV light. Commercially available reagents and solvents of the chemically pure grade were used in the syntheses without additional purification. The characteristics of compounds **1**, **4 a**,**i**,**l** [29], **1b** [30], **1d**,**h** [31], **4d** [7], **1**, **4e** [32], and **4h** [33] matched the literature.

Synthesis of the 1-(2-Hydroxyphenyl)-3-phenylprop-2-en-1-one Derivatives 1a-l (General Method). Aromatic aldehyde (1 mmol) was added to a solution of 4-R-2-hydroxyacetophenone (1 mmol) and KOH (0.28 g, 5 mmol) in MeOH (3 ml), followed by stirring at room temperature for 10-20 h. For poorly soluble substrates, the solvent was 80% aqueous *N*-methylpyrrolidone instead of MeOH. The mixture was neutralized with 5% HCl to pH 4-6. The precipitate was filtered off and purified by flash chromatography (eluent $CHCl_3$ or 1% 2-PrOH in $CHCl_3$). The chalcones **1a-l** were obtained in 60-90% yield.

1-[4-(Benzyloxy)-2-hydroxyphenyl]-3-phenyl-2-propen-1-one (1f). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.23 (2H, s, CH_2); 6.63 (1H, d, *J* = 2.5, H-3'); 6.66 (1H, dd, *J* = 9.0, *J* = 2.5, H-5'); 7.36 (1H, t, *J* = 7.2, H Ph); 7.40-7.44 (2H, m, H Ph); 7.47-7.49 (5H, m, H Ph); 7.84 (1H, d, *J* = 15.5, α-CH); 7.90-7.84 (2H, m, H Ph); 8.03 (1H, d, *J* = 15.5, β-CH); 8.31 (1H, d, *J* = 9.0, H-6'); 13.41 (1H, s, OH). Mass spectrum, *m*/*z*: 331.3 $[M+H]^+$, 353.2 $[M+Na]^+$. Found, %: C 79.96; H 5.67. $C_{22}H_{18}O_3$. Calculated, %: C 79.98; H 5.49.

1-[2-Hydroxy-4-(4-methoxybenzyloxy)phenyl]-3-phenyl-2-propen-1-one (1g). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.75 (3H, s, OCH_3); 5.13 (2H, s, CH_2); 6.58 (1H, d, *J* = 2.5, H-3'); 6.61 (1H, dd, *J* = 8.8, *J* = 2.4,

H-5'); 6.94 (2H, d, *J* = 8.6, H-3,5 Ar); 7.38 (2H, d, *J* = 8.6, H-2,6 Ar); 7.41-7.49 (3H, m, H Ph); 7.81 (1H, d, *J* = 15.5, α-CH); 7.85-7.92 (2H, m, H Ph); 8.00 (1H, d, *J* = 15.5, β-CH); 8.27 (1H, d, *J* = 9.0, H-6'). Mass spectrum, *m*/*z*: 361.4 $[M+H]^+$, 383.5 $[M+Na]^+$, 400.8 $[M+K]^+$. Found, %: C 76.34; H 5.61. $C_{23}H_{20}O_4$. Calculated, %: C 76.65; H 5.59.

3-[4-(4-Methoxybenzyloxy)phenyl]-3-phenyl-2-propen-1-one (1k). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.74 (3H, s, OCH_3); 5.09 (2H, s, CH_2); 6.90-7.01 (4H, m, H Ar); 7.08 (2H, d, *J* = 8.8, H-2,6 Ar); 7.38 (2H, d, *J* = 8.8, H-2,6 Ar); 7.54 (1H, td, *J* = 7.6, *J* = 1.7, H-5'); 7.81 (1H, d, *J* = 15.5, α-CH); 7.84-7.92 (3H, m, H-3',4', β-CH); 8.24 (1H, dd, *J* = 8.6, *J* = 1.6, H-6'). Mass spectrum, *m*/*z*: 361.4 $[M+H]^+$, 400.8 $[M+K]^+$. Found, %: C 76.69; H 5.65. $C_{23}H_{20}O_4$. Calculated, %: C 76.65; H 5.59.

Synthesis of the 3-Hydroxy-2-phenyl-4*H*-chromen-4-one Derivatives 4a-l (General Method). A 50% H_2O_2 solution (0.28 ml, 5 mmol) was added dropwise with stirring to a solution of the chalcone **1a-l** (1 mmol) and NaOH (0.20 g, 5 mmol) in 80% aqueous MeOH (20 ml). The solution was stirred for 2-15 h. After the reaction completion, the mixture was neutralized with 5% HCl to pH 4-6 and evaporated at reduced pressure and at temperature not exceeding 40°C. The residue was filtered off and recrystallized from aqueous MeOH. Additional purification by repeated crystallization from THF–hexane or 2-PrOH–hexane mixtures was needed for obtaining pure samples of compounds **4d**,**e**. The yield of these compounds was determined by ^{1}H NMR spectroscopy as the combined content of the title compound in all fractions.

7-(Benzyloxy)-3-hydroxy-2-phenyl-4*H*-chromen-4-one (4f). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.20 (2H, s, CH_2); 7.13 (1H, d, *J* = 8.7, H-6); 7.34-7.38 (2H, m, H Ph); 7.46-7.55 (7H, m, H Ph); 7.74 (1H, d, *J* = 8.7, H-5); 8.22 (2H, d, *J* = 7.6, H-2',6'); 9.50 (1H, br. s, OH). Mass spectrum, *m*/*z*: 345.2 $[M+H]^+$, 367.2 $[M+Na]^+$. Found, %: C 76.90; H 4.72. $C_{22}H_{16}O_4$. Calculated, %: C 76.73; H 4.68.

3-Hydroxy-7-(4-methoxybenzyloxy)-2-phenyl-4*H*-chromen-4-one (4g). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.75 (3H, s, OCH_3); 5.17 (2H, s, CH_2); 6.95 (2H, d, *J* = 8.6, H-3,5 Ar); 7.07 (1H, dd, *J* = 9.0, *J* = 2.4, H-6); 7.36 (1H, d, *J* = 2.3, H-8); 7.42 (2H, d, *J* = 8.6, H-2,6 Ar); 7.48 (1H, t, *J* = 7.3, H-4'); 7.52-7.57 (2H, m, H-3',5'); 7.99 (1H, d, *J* = 8.9, H-5); 8.19 (2H, d, *J* = 8.4, H-2',6'); 9.42 (1H, br. s, OH). Mass spectrum, *m*/*z*: 375.5 $[M+H]^+$, 397.5 $[M+Na]^+$, 413.5 $[M+K]^+$. Found, %: C 73.56; H 4.87. $C_{23}H_{18}O_5$. Calculated, %: C 73.79; H 4.85.

3-Hydroxy-2-[4-(4-methoxybenzyloxy)phenyl]-4*H*-chromen-4-one (4k). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.77 (3H, s, OCH_3); 5.13 (2H, s, CH_2); 6.97 (2H, d, *J* = 8.1, H-3,5 Ar); 7.21 (2H, d, *J* = 8.6, H-3',5'); 7.43 (2H, d, *J* = 8.1, H-2,6 Ar); 7.47 (1H, t, *J* = 7.2, H-6); 7.74-7.83 (2H, m, H-7,8); 8.12 (1H, d, *J* = 7.8, H-5); 8.21 (2H, d, *J* = 8.5, H-2',6'); 9.46 (1H, br. s, OH). Mass spectrum, *m*/*z*: 375.02 $[M+H]^+$, 396.98 $[M+Na]^+$, 412.99 $[M+K]^+$. Found, %: C 73.69; H 4.86. $C_{23}H_{18}O_5$. Calculated, %: C 73.79; H 4.85.

Quantum-chemical calculations were performed with the MOPAC 2009 software package [34]. Preliminary calculations of molecular geometry at equilibrium and estimation of electron density distribution were performed with the semiempirical RM1 method [35]. Further geometry optimization and calculation of thermodynamic characteristics (the entalphy and enthropy of the studied compounds and intermediates) was performed with the PM6 method [26]. Both methods were used in the software package. The nonspecific interactions of the reaction system with aqueous medium were accounted for by using the COSMO method [36].

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