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DFT/B3LYP calculated bond-dissociation enthalpies, radical-scavenging and antioxidant activities of natural-like coumarins

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Dedicated to Acad. Dimiter Ivanov on the occasion of his 120th birth anniversary

Bond dissociation enthalpies (BDEs) of O-H groups of a set of hydroxy- and dihydroxy-4-methylcoumarins have been calculated in gas phase and in acetone by means of density functional theory calculations at B3LYP/6-31+G(d,p) level. The study has been done to determine the capacity of bond-dissociation enthalpy to explain the observed radical-scavenging and chain-breaking antioxidant activities of the studied coumarins. DPPH radical scavenging activity (RSA) in acetone solution [as %RSA and stoichiometry coefficient (n) for the fast (2 min) and total (20 min) kinetics] and the chain-breaking antioxidant activity (as protection factor, PF) during bulk phase lipid autoxidation have been used in the experimental study. The experimental results for the studied compounds show that the two phenolic groups at *ortho* position work in tandem, while the same at *meta* position work independent of each other. According to the theoretical results, the substitution in the benzene ring of the coumarin system is very important for the chain-breaking antioxidant activity. At the same time, theoretical calculations reveal that the introduction of methyl group and/or various substituents at the C-3 and C-4 positions of the pyrone ring affects the BDEs insignificantly. Interestingly, the radical scavenging activity towards DPPH radical of 7,8-dihydroxy-4-methylcoumarins are much higher than that of the 6,7-dihydroxy-4-methylcoumarins, 5,7-dihydroxy-4-methylcoumarin and 7-hydroxy-4-methylcoumarin. Differences in RSA of studied coumarins could be explained with the solvent effect of acetone. Our findings revealed that BDE can serve as a probe for radical scavenging and antioxidant activities and even have predictive capacity, but for some tiny effects a precise description of the solvent effects is required.

Key words: coumarins, hydroxycoumarins, DFT, bond-dissociation enthalpy, chain- breaking antioxidant activity, radical-scavenging activity

INTRODUCTION

In nature, coumarins are abundantly found in plants and are formed via the shikimate pathway [1,2]. Natural coumarins and their synthetic analogues manifest a wide range of activities such as anticoagulant, antitumor, antiviral, anti-inflammatory, antimicrobial, antioxidant (radical-scavenging), and enzyme inhibition activity [3-6]. The presence of different substituents on the coumarin ring system strongly influences the antioxidant and biological activities of the resulting derivatives [5,7]. The pharmacological applications of coumarins are limited by the tendency to form mutagenic and toxic C-3, C-4 coumarin epoxide intermediates during their metabolic degradation [8,9]. Introduction of methyl group at the C-4 position is a possible way to prevent formation of these dangerous C-3, C-4 epoxides during the metabolic degradation of the coumarins [10]. In a detailed investigation of the structure-activity relationship of dihydroxy-4-methylcoumarins by Kancheva *et al.* [11], the effects of the substituents in both rings of the coumarin system have been substantiated: the substituents in the benzene ring are responsible for the antioxidant activity of the studied hydroxy-4-methylcoumains, while the effect of substituents in the pyrone ring (at positions C-3 and C-4) is insignificant for the biological activity.

In the present study, a set of coumarin derivatives has been selected in order to correlate

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the structural differences with alternations in the radical scavenging and chain-breaking antioxidant activities (taking in mind the above mentioned parameters) by means of DFT calculation. The following structural modifications have been taken into consideration: number and positions of the OH-groups, presence or absence of the methyl group at the C-4 position and different substituents at the C-3 position. The chief emphasis of our investigation has been towards the direct hydrogen atom transfer between the antioxidant and the active radical. The descriptor related to this mechanism is the bond-dissociation enthalpy (BDE). The theoretical (*ab initio* and DFT) calculations are helpful in the explanation of the structure-activity relationship [9,12,13]. Successful applications of BDE on polyphenolic compounds as theoretical descriptors of antioxidant activity/efficiency has already been reported by us [14,15]. It is well known that the antioxidant power of phytochemicals (including coumarins), as well as other biochemical properties, depend not only on the substitution in the parent molecule(s), but also on the reaction medium and from the nature of the involved free radicals/reactive species [16]. Therefore, the structure-activity relationship needs to be explored in different environments. Taking into account the report of Yordanov [17] about the higher stability of DPPH radical in acetone solution than in ethanol, the DPPH test was run in acetone solution. Chain-breaking antioxidant activity of the studied coumarins was tested during bulk phase lipid autoxidation.

EXPERIMENTAL AND COMPUTATIONAL DETAILS

Chemicals

All coumarins used in the experimental study (Fig. 1, Table 1) were synthesized and characterized at the Department of Chemistry, University of Delhi, Delhi as described previously [18-21]. DPPH was purchased from Sigma-Aldrich.

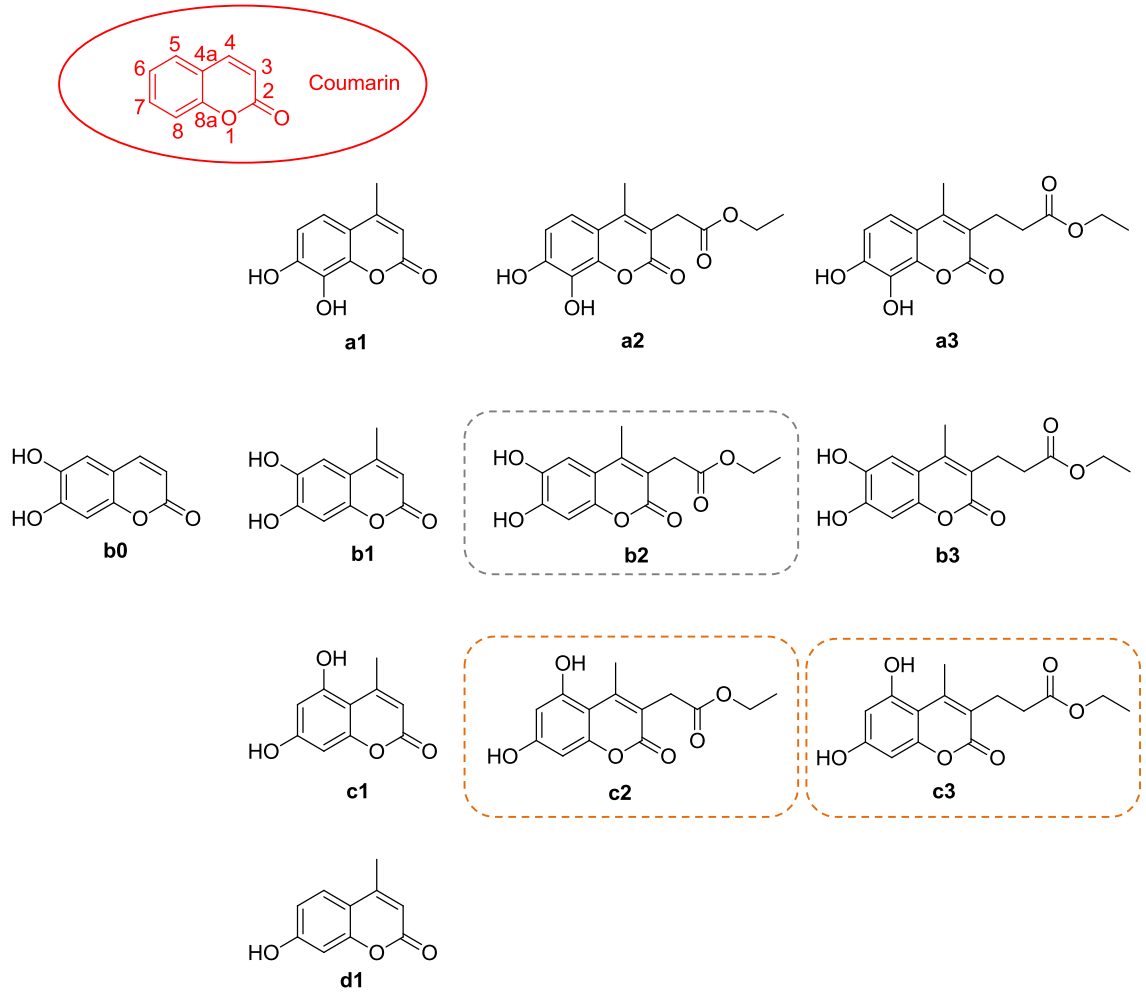


Fig. 1. Structures of coumarin and compounds **a1-a3**, **b0-b3**, **c1-c3**, **d1**. In rounded rectangle boxes are structures of the compounds for which only theoretical data are available (grey box) or for which experimental results are derived after theoretical predictions (orange boxes).

Table 1. Compound names.

Coumarin	2H-chromen-2-one
a1	7,8-dihydroxy-4-methyl-2H-chromen-2-one
a2	ethyl 2(7,8-dihydroxy-4-methyl-2-oxo-2H-chromen-3-yl)acetate
a3	ethyl 3-(7,8-dihydroxy-4-methyl-2-oxo-2H-chromen-3-yl)propanoate
b0	6,7-dihydroxy-2H-chromen-2-one
b1	6,7-dihydroxy-4-methyl-2H-chromen-2-one
b2	ethyl 2(6,7-dihydroxy-4-methyl-2-oxo-2H-chromen-3-yl)acetate
b3	ethyl 3-(6,7-dihydroxy-4-methyl-2-oxo-2H-chromen-3-yl)propanoate
c1	5,7-dihydroxy-4-methyl-2H-chromen-2-one
c2	ethyl 2(5,7-dihydroxy-4-methyl-2-oxo-2H-chromen-3-yl)acetate
c3	ethyl 3-(5,7-dihydroxy-4-methyl-2-oxo-2H-chromen-3-yl)propanoate
d1	7-hydroxy-4-methyl-2H-chromen-2-one

Screening for free radical scavengers by DPPH test

Kinetics of DPPH absorbance decrease for a quantitative determination of radical scavenging activity at the ratio antioxidant (AH) and DPPH [AH]/[DPPH] = 0.40 and physiological temperature 37^{o}C was studied. For experimental details, please see ref.10. The main kinetic parameters for the fast kinetics (Δt=2 min) $\%RSA_{fast}$ and n_{fast} and for the total kinetics (Δt=20 min) $\%RSA_{tot}$ and n_{tot} were determined by the following formulae:

$$\%RSA = [(Abs_0 - Abs_t)/Abs_0] \times 100,$$

$$n = [(Abs_0 - Abs_t)]/\varepsilon[AH],$$

where: Abs_0 and Abs_t stay for the DPPH absorption at 517 nm for time t=0 and t=2 min (fast kinetics) or t=20 min (total kinetics), n is the stoichiometric coefficient, meaning how many DPPH radicals were trapped from 1 molecule of AH, molar extinction coefficient $\varepsilon = 1.2 \times 10^4\ M^{-1}s^{-1}$.

Chain-breaking antioxidant activity of coumarins under study presented as protection factor (PF), means how many times the added antioxidant AH can increase the oxidation stability of lipid substrate was studied as described in our earlier publication [11]. Here we report new data about $\mathbf{a_3}$ and $\mathbf{b_3}$ coumarins.

Computational details

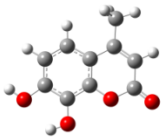
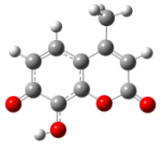
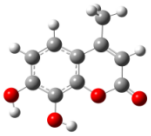
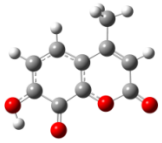
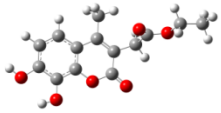
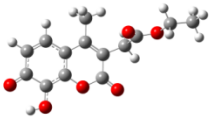
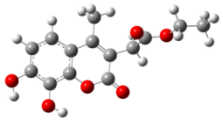
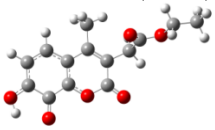
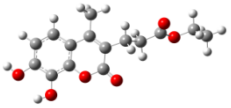
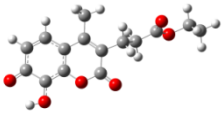
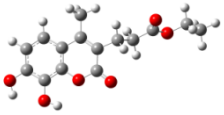
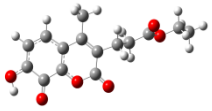
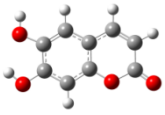
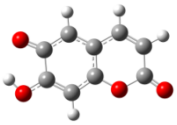
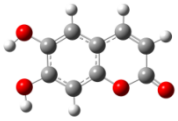
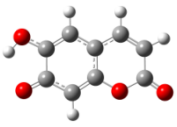
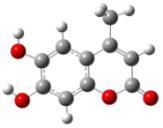
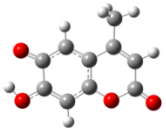
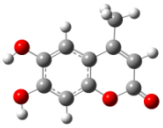
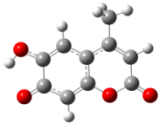
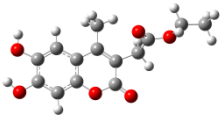
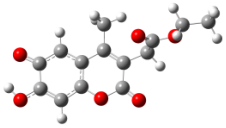
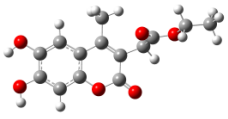
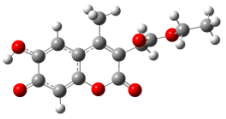
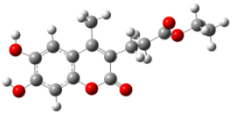
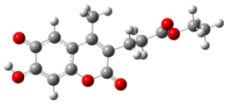
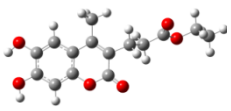
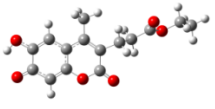
As a descriptor of antiradical/antioxidant activity, calculated homolytic bond dissociation enthalpy (BDE) was utilized. B3LYP calculations were chosen for this study because this functional provides reliable geometries, frequencies, and bond lengths [22]. The geometries of compounds studied and their radicals were optimized using unrestricted open-shell approach (UB3LYP) and 6-31+G(d,p) basis set [23-25] without symmetry constraints with the default convergence criteria. Frequency calculations at the same level of theory were carried out to confirm that the obtained structures correspond to energy minima. Unscaled thermal corrections to enthalpy were added to the total energy values. The BDEs for the generation of the respective radicals from the parent compounds are calculated by the formula $BDE = H_{298}(A\bullet) + E_T(H\bullet) - H_{298}(AH)$ where $H_{298}(A\bullet)$ and $H_{298}(AH)$ are enthalpies calculated at 298 K for radical species A• and neutral molecule AH, respectively, and $E_T(H\bullet)$ (calculated total energy of H•) is -313.93 kcal mol^{-1}. In order to take into account the solvent effect, the integral equation formalism (IEF) of the polarizable continuum model (PCM) [26-28] was employed for acetone and all the structures were optimized in this surrounding environment. All quantum chemical calculations were carried out using GAUSSIAN 09 program package [29].

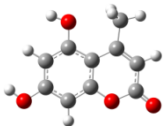
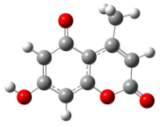
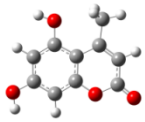
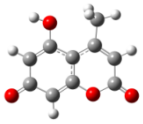
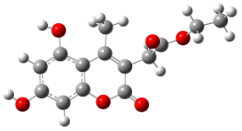
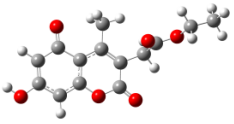
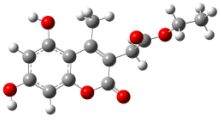
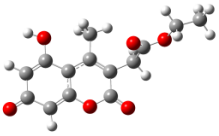
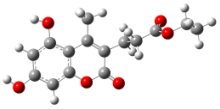
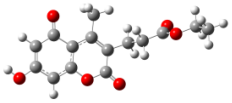
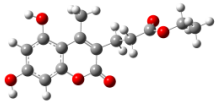
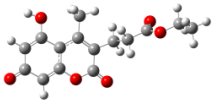
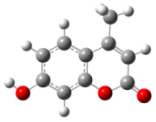
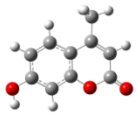
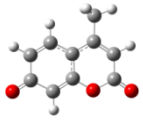
RESULTS AND DISCUSSION

UB3LYP/6-31+G(d,p) calculated enthalpies (H_{298}) at 298 K, enthalpy differences (ΔH_{298}) between rotamers of the compounds studied and their radicals and bond dissociation enthalpy (BDE) in gas phase and in solvent acetone are listed in Table 2. For the coumarins belonging to group **a** and **b,** only rotamers with intramolecular hydrogen bonds are studied. These rotamers differ in the position of the hydrogen atoms from the hydroxyl groups in the coumarin moiety. The structures of the denoted "rotamers 1 & 2" are shown in Table 2. Two rotamers of compounds from group **c** with different orientation of the OH hydrogen atoms in position 7 are also considered. In gas phase the following relations can be noticed: for all the compounds, rotamer 2 is more stable than rotamer 1, and the BDEs of the radicals formed from this rotamer are considered (in spite of the lower BDE values characterizing the radical, formed from rota-

mer 1). The enthalpy difference between the rotamers of group **a** compounds is about 5 kcal mol^{-1}, of group **c** compounds is about 1 kcal mol^{-1}, while rotamers of group **b** compounds have almost equal

Table 2.UB3LYP/6-31+G(d,p) calculated enthalpies (H_{298}) at 298 K (in Hartree), enthalpy differences (ΔH_{298}) between rotamers of compounds studied and their radicals (in kcal mol^{-1}) and bond dissociation enthalpy (BDE) (in kcal mol^{-1}). The values in acetone are given in parentheses.

	Rotamer 1	**Radical 1: 7(7,8)**	**Rotamer 2**	**Radical 2: 8(7,8)**
a1				
	H_{298}=-686.645831 (-686.661963) ΔH_{298}=5.50 (1.86)	H_{298}=-686.028641 (-686.041754) BDE=73.37 (75.26)	H_{298} =-686.654589 (-686.664920) ΔH_{298}=0.00 (0.00)	H_{298}=-686.030393 (-686.044250) BDE=77.76 (75.54)
a2				
	H_{298}=-993.064035 (-993.081013) ΔH_{298}=5.26 (1.94)	H_{298}=-992.447700 (-992.461856) BDE =72.83 (74.59)	H_{298}=-993.072418 (-993.084112) ΔH_{298}=0.00 (0.00)	H_{298}=-992.448975 (-992.464084) BDE =77.29 (75.14)
a3				
	H_{298}=-1032.352843 (-1032.369799) ΔH_{298}=5.18 (2.86)	H_{298}=-1031.736581 (-1031.752441) BDE = 72.78 (73.47)	H_{298}=-1032.361095 (-1032.37436) ΔH_{298}=0.00 (0.00)	H_{298}=-1031.737713 (-1031.754311) BDE= 77.25 (75.15)
	Rotamer 1	**Radical 1: 6(6,7)**	**Rotamer 2**	**Radical 2: 7(6,7)**
b0				
	H_{298}=-647.357275 (-647.371649) ΔH_{298}=0.06 (0.00)	H_{298}=-646.741251 (-646.751778) BDE =72.63 (75.04)	H_{298}=-647.357375 (-647.371162) ΔH_{298}=0.00 (0.31)	H_{298}= -646.740335 (-646.751314) BDE =73.21 (75.33)
b1				
	H_{298}=-686.650881 (-686.665921) ΔH_{298}=0.26 (0.00)	H_{298}=-686.035698 (-686.046682) BDE =72.11(74.65)	H_{298}=-686.651300 (-686.665549) ΔH_{298}=0.00 (0.23)	H_{298}=-686.034081 (-686.045675) BDE =73.38 (75.04)
b2				
	H_{298}=-993.069272 (-993.084718) ΔH_{298}=0.12 (0.00)	H_{298}=-992.454061 (-992.466346) BDE=72.12 (74.10)	H_{298}=-993.069462 (-993.084623) ΔH_{298}=0.00 (0.06)	H_{298}=-992.453109 (-992.465771) BDE=72.84 (74.40)
b3				
	H_{298}=-1032.357886 (-1032.375617) ΔH_{298}=0.21 (0.00)	H_{298}=-1031.742831 (-1031.756799) BDE=72.03 (74.38)	H_{298}=-1032.358213 (-1032.375137) ΔH_{298}=0.00 (0.30)	H_{298}=-1031.742023 (-1031.756515) BDE= 72.74 (74.26)

	Rotamer 1	Radical 1: 5(5,7)	Rotamer 2	Radical 2: 7(5,7)
c1				
	H_{298}=-686.647224 (-686.661877) ΔH_{298}=1.15 (0.27)	H_{298}=-686.022300 (-686.034022) BDE=78.22 (80.05)	H_{298}=-686.649058 (-686.662311) ΔH_{298}=0.00 (0.00)	H_{298}= -686.016344 (-686.029859) BDE=81.96 (82.67)
c2				
	H_{298}=-993.064037 (-993.081188) ΔH_{298}=1.13 (0.26)	H_{298}=-992.440251 (-992.454364) BDE=77.51 (79.41)	H_{298}=-993.065837 (-993.08161) ΔH_{298}=0.00 (0.00)	H_{298}= -992.434172 (-992.449879) BDE=81.32 (82.22)
c3				
	H_{298}=-1032.352611 (-1032.369611) ΔH_{298}= 1.12 (0.29)	H_{298}=-1031.729210 (-1031.74345) BDE=77.26 (78.99)	H_{298}=-1032.354388 (-1032.370074) ΔH_{298}=0.00 (0.00)	H_{298}=-1031.723117 (-1031.739294) BDE=81.09 (81.60)
	Rotamer 1		**Rotamer 2**	**Radical: 7**
d1				
	H_{298}=-611.431360 (-611.443368) ΔH_{298}=0.44 (0.03)		H_{298}=-611.432056 (-611.443410) ΔH_{298}=0.00 (0.00)	H_{298}=-610.799536 (-610.811495) BDE=82.55 (82.57)

enthalpies (ΔH_{298}=0.06÷0.21 kcal mol^{-1}). For **d1** the difference is also very low – 0.44 kcal mol^{-1}. In acetone medium the enthalpy difference between the rotamers of the compounds from **a** and **c** groups decreases but with different scale, the rotamers 1 of group **b** are preferred with very low ΔH_{298} (0.06÷0.31 kcal mol^{-1}), for **d1** both rotamers are isoenergetic (ΔH_{298}=0.03 kcal mol^{-1}). It can be concluded that the addition of acetone (as surrounding environment) equalize the BDEs for both OH-groups of the dihydroxy compounds as for compounds **c** this trend is not so strong.

The BDEs for the preferred rotamers of compounds **a1-a3**, **c1-c3**, both rotamers of compounds from **b** group and of **d1** are presented graphically on Fig. 2. The values in gas phase and in acetone are compared. In gas phase compounds from **b** group are characterized with the lowest BDE values, followed by **a** group with higher BDEs, while the compounds with OH-groups in positions 5,7 (**c1-c3**) and with one OH group (**d1**) are with highest BDEs. The substituent in position 3 does not affect ($BDE_{6(6,7)}$) or affect weakly the BDEs, as in almost all cases (exception – group **c**) the lengthening of substituent's chain in this position leads to lower BDE values. When the solvent is taken into account, the BDEs of compounds **a1-a3** decrease, the BDE of **d1** is not affected, while the BDEs of compounds **b** and **c** increase (exception - **c2**). As a result, the BDEs of **a** and **b** groups are equalized in acetone medium, but the separation of compounds in two groups (with and without catechol moiety) is preserved, i. e. the BDE values of **a** and **b** groups remain lower than those of **c** and **d** groups. The observed tendency is in accordance with the conclusion of Zhang *et al.* that the catechol moiety in the coumarins is a beneficial structural factor that reduces BDE and the coumarins with this fragment are strong antioxidants [13].

The effect of the CH_3-group on the BDE can be estimated from the comparison of the BDEs of **b0** and **b1**. The presence of CH_3-group at position 4 in the tested coumarins does not act equally on both the OH-groups in gas phase: **b0** is characterized with higher $BDE_{6(6,7)}$ and lower $BDE_{7(6,7)}$ in comparison to **b1**, while in acetone both OH-groups of **b1** have lower BDEs than **b0**.

The BDE of the more stable rotamers (respectively in gas phase and in solvent acetone)

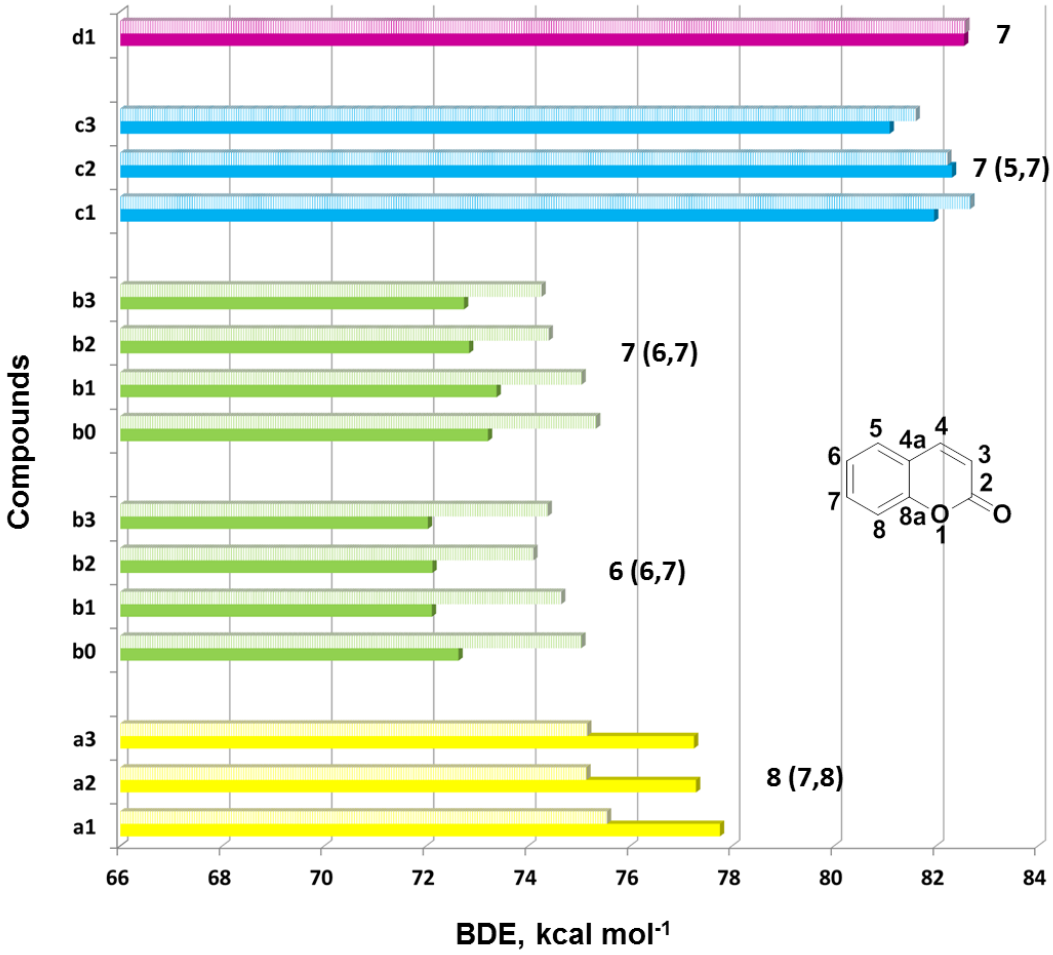


Fig. 2. Selected BDEs (in kcal mol^{-1}) in gas phase (solid fill) and in acetone (pattern fill). The position of OH group from which H atom is abstracted and the positions of OH groups in the coumarin main structure (in parentheses) are denoted.

Table 3. Theoretical parameters (BDE in gas phase and in acetone) and the main experimental kinetic parameters: antioxidant efficiency, presented as a protection factor (PF) during lipid autoxidation, % RSA and stoihiometry (n) for the fast (t=2 min) and total (t=20 min) kinetics of DPPH radical absorption decrease at 516-517 nm.

	BDE (gas phase), kcal mol^{-1}	**PF**	**BDE (acetone)** kcal mol^{-1}	**RSA_{fast}, %**	**n_{fast}, $M^{-1}s^{-1}$**	**RSA_{tot}, %**	**n_{tot}, $M^{-1}s^{-1}$**
a1	77.76	1.3	75.54	35.8	0.9	49.1	1.1
a2	77.29	1.5	75.14	-	-	-	-
a3	77.25	1.4	75.15	48.8	1.2	64.2	1.6
b0	73.21[a]	3.7	75.04[b]	-	-	-	-
b1	73.38[a]	3.4	74.65[b]	16.3	0.4	17.3	0.4
b3	72.74[a]	3.4	74.38[b]	18.6	0.5	21.2	0.5
c1	81.96	1.2	82.67	3.0	0.1	3.0	0.1
c2	81.32	1.2	82.22	-	-	-	-
c3	81.09	1.1	81.60	-	-	-	-
d1	82.55	1.0	82.57	2.2	0.1	2.2	0.1

[a] - BDE 7(6,7); [b] - BDE 6(6,7).

for each structure is compared to the experimentally derived data in Table 3. The presented experimental data are chain-breaking antioxidant activity (as PF) and DPPH scavenging (as %RSA and n) for the fast and total kinetics. The protection factors (PF) of **b0**, **b1** and **b3** are in the range 3.4-3.7 while the rest of compounds are characterized with values in the range of 1.0-1.5, i.e. compounds from **b**-group have

the highest antioxidant efficiency during lipid autoxidation. The gas phase calculated BDEs are in agreement with these results: the compounds with high PF have low BDE values and *vice versa*. The coumarins from group **a** (**a3** and **a1**) demonstrate strong RSA (%RSA > 40%), coumarins from group **b** (**b1** and **b3**) – moderate RSA (15%< %RSA < 40%), **c1** and **d1** – weak RSA (%RSA < 15%). The much lower value of %RSA for **c1** (*meta*-dihydroxy-coumarin) than *ortho*-dihydroxy-coumarins is not unforeseen considering the position of OH groups. The OH groups of compound **c** react individually with DPPH radical, not in tandem (like *ortho*-dihydroxy-coumarins) and %RSA is close to the value for the mono-hydroxycoumarin (**d1**). The compounds from **b** group are characterized with lower $\%RSA_{tot}$ values (17.3 and 21.2) than those from **a** group (41.9 and 64.2) inspite of the *ortho* positioning of the OH-groups in all of them. The BDEs in acetone for both groups **a** and **b** of *ortho*-dihydroxy-coumarins are close, all values being in the range of 74.38-75.54 kcal mol^{-1}. The failure of the calculations to distinguish these groups could be explained with the incomplete description of the solvent-solute interactions by the model used (PCM). The difference in the RSAs of compounds from **a** and **b** groups is probably due to the formation of different active intermediates from 7,8-diOH and 6,7-diOH, which react with different rates with DPPH. Monophenolic coumarin **d1** in the cross-recombination reaction form inactive products. *Meta*-dihydroxy coumarin reacts as two mono-phenolic antioxidants. Each OH-group reacts individually (not in tandem as *ortho*-substituted) and thus the formation of active intermediates cannot increase their RSA. *Meta*-dihydroxy coumarin **c1** shows RSA close to that of the monophenolic coumarin and much lower than that of *ortho*-dihydroxycoumarins. The stoichiometric coefficients n_{tot} for *ortho*-dihydroxycoumarins (group **b)** are lower than 1 (0.4 and 0.5 for **b1** and **b3** respectively) and much lower for **c1** and **d1** (n_{tot} = 0.1). Compounds **a1** and **a3** are characterized with different stoichiometric coefficients n_{tot} - 1.1 and 1.6 $M^{-1}s^{-1}$. The proposed mechanisms which explain the different values of the experimentally derived stoichiometry coefficient for **a1** and **a3** are listed in Table 4. One molecule **a1** can trap one DPPH radical (n = 1), while one molecule **a3** can trap 1.5 DPPH radicals (n = 1.5).

DFT calculated BDEs in gas phase and in acetone are able to distinguish the effects of the substituents at positions 3 and 4, but failed in the description of the activity of the systems sensible to the solvent effects (*ortho*-dihydroxy-coumarins from **a** and **b** groups).

CONCLUSION

In this study, the power (capacity) of DFT calculations for the explanation of radical-scavenging and antioxidant activities of mono- and dihydroxycoumarins is tested. A relatively good correlation between antioxidant efficiency (PF) of lipid autoxidation and O-H BDEs in gas phase is found. The studied hydroxycoumarins are divided into three groups: strong (PF=3.4-3.7, BDE=72.74-73.21 kcal mol^{-1}), moderate (PF=1.3-1.5, BDE=77.25-77.76 kcal mol^{-1}) and weak antioxidants (PF=1.0-1.2, BDE=81.96-82.55 kcal mol^{-1}), i.e. the compounds with high PF have low BDE values and *vice versa*. We observed that in acetone BDE values are grouped into two groups: 1) *ortho*-dihydroxy-coumarins **a1-a3** and **b0-b3** (BDE=74.10-75.54 kcal mol^{-1}) and 2) *meta*-dihydroxy-coumarins **c1-c3** and monohydroxy-coumarin **d1** (BDE=81.60-82.64 kcal mol^{-1}). Calculated BDEs in acetone for compounds of the series **a** and **b** are close and do not explain the difference in the experimentally derived RSA and stoichiometry coefficient n for the fast and total kinetics of the decreased DPPH radical absorption of the *ortho*-dihydroxycoumarins. We propose that

Table 4. The proposed mechanism of action between DPPH radical and coumarins of group **a** ($\mathbf{a_1}$ and $\mathbf{a_3}$) for explanation of the experimentally observed total stoichiometry (n_{tot}).

	n_{tot}, $M^{-1}s^{-1}$	Mechanism A_1H and A_3H- the correspond coumarins; A_1•and A_3•- coumarins' radicals; A-A – unactive dimer	Stoichiometry coefficient for the proposed mechanism
a1	1.1	$A_1H + DPPH• \rightarrow A_1• + DPPH – H$ x2; H atom transfer $2\ A_1• \rightarrow A_1\text{-}A_1$; homo-recombinaton reaction **$2\ A_1H + 2DPPH• \rightarrow 2DPPH – H + A_1\text{-}A_1$**	n = 1
a3	1.6	$A_3H + DPPH• \rightarrow A_3•\ + DPPH – H$ x2; H atom transfer $A_3• + DPPH• \rightarrow A_3\text{-}DPPH$; cross-recombination reaction $2\ A_3• \rightarrow A_3\text{-}A_3$; homo-recombinaton reaction **$2\ A_3H + 3DPPH• \rightarrow 2DPPH – H + A_3\text{-}DPPH + A_3\text{-}A_3$**	n = 1.5

DFT calculated BDEs have the potential as a probe for radical scavenging and antioxidant activities but more precise description of the solvent effects where the specific interactions are taken into account is highly recommended and the results must be handled carefully.

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DFT/B3LYP ИЗЧИСЛИТЕЛНИ ЕНТАЛПИИ НА ДИСОЦИАЦИЯ НА ВРЪЗКА, РАДИКАЛОВО-УЛОВИТЕЛНА И АНТИОКСИДАНТНА АКТИВНОСТ НА СИНТЕТИЧНИ АНАЛОЗИ НА ПРИРОДНИ КУМАРИНИ

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(Резюме)

Енталпиите на дисоциация на връзка (ЕДВ) в О-Н групи на серия от хидрокси и дихидрокси-4-метил кумарини са изчислени в газова фаза и в ацетон чрез използване на теория на функционала на плътността на B3LYP/6-31+G(d,p) ниво. Изследването е проведено с цел да се определи способността на енталпиите на дисоциация на връзка да обяснят наблюдаваните радикалоулавяща и прекъсваща окислителната верига антиоксидантна активности на изследваните кумарини. При експерименталното изследване са използвани дифенилпикрилхидразил (ДФПХ) радикалоулавяща активност в разтвор на ацетон [като %RSA и стехиометричен коефициент n за бърза (2 мин.) и тотална (20 мин.) кинетика] и прекъсваща окислителната верига антиоксидантна активност (като фактор на стабилизиране, PF) по време на липидно автоокисление в хомогенна среда. Експерименталните резултати за изследваните съединения показват, че двете фенолни групи в *орто* положение действат съвместно, докато в *мета* положение не зависят една от друга. Според теоретичните данни заместването в бензеновия пръстен на кумариновата система е много важно за прекъсващата окислителната верига антиоксидантна активност. Също така според теоретичните изчисления въвеждането на метилова група и/или други заместители в положение С-4 и С-3 на пироновия пръстен влияе върху ЕДВ незначително. Интересното е, че радикалоулавящата активност (РУА) спрямо ДФПХ радикал на 7,8-дихидрокси-4-метил-кумарините е много по-висока от тази на 6,7-дихидрокси-4-метил-кумарините, 5,7-мета-дихидрокси-4-метил-кумарина и 7-хидрокси-4-метил-кумарина. Разликите в РУА на изследваните съединения вероятно се дължи на влиянието на разтворителя (ацетон). ЕДВ може да се използва като мярка за радикалоулавяща и прекъсваща окислителната верига антиоксидантна активности и има предсказваща способност, но за някои фини ефекти се налага да се отчитат детайлно ефектите на разтворителя.