



Chemical reactivity and stability predictions of some coumarins by means of DFT calculations

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Article info

Received: 31/10/2014
Accepted: 18/11/2014

Keywords:

coumarins, chemical reactivity descriptors, DFT studies.

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Abstract: Three synthesized coumarin derivatives were studied for their quantum-chemical properties. These compounds are commonly used as starting material for many syntheses of biologically active compounds. In order to explore the theoretical-experimental consistency, DFT global chemical reactivity descriptors (chemical hardness, total energy, electronic chemical potential and electrophilicity) were calculated for these compounds using standard Spartan 10 software. Complete geometry optimization was carried out by B3LYP/6-31G* level of theory. Some quantum-chemical calculations correlated well with experimental work; mechanisms of reactions with these compounds as starting material were partially explained by these calculated parameters. These calculations were once more proof that by means of mathematical models it is possible to describe chemical interactions and simulate the behavior of chemical systems – molecules and reactions.

INTRODUCTION

Density Functional Theory (DFT) has been accepted as reliable and effective approach for the computation of molecular structure, vibration frequencies and energies of chemical reactions (Beyramabadi, Morsali, 2011; Mebi, 2011; Monajjemi, Sayadian, Zare, et al., 2011; Kadhum, Al-Amiery, Shikara, et al., 2011). It provides an efficient method to include correlation energy in electronic calculations (Koch, Holthausen, 2011). In addition it constitutes a solid support to reactivity models (Pearson, 1997). Reactivity of the molecule is always governed by its electronic properties and kinetic and thermodynamic stability.

4-Hydroxycoumarin and some simple derivatives are commonly used as starting material for many chemical reactions. Great number of syntheses of biologically active compounds, starting from 4-hydroxycoumarin, has been

described in literature. These reactions are characterized to follow mechanism of electrophilic substitution where 4-hydroxycoumarin reacts with strong electron withdrawing groups (Završnik, Špirtović-Halilović, Softić, 2011). Acetylated derivative of 4-hydroxycoumarin (3-acetyl-4-hydroxycoumarin) is involved in some reactions of nucleophilic addition (Završnik, Špirtović-Halilović, Softić, 2011; Špirtović-Halilović, Salihović, Džudžević-Čančar, et al., 2014). Also, there are references on 4-hydroxy-3-iminomethylencoumarin as a precursor undergoing hydrolysis, thus giving next precursor involved in various synthetic routes (Završnik, Bašić, Bečić, et al., 2003).

In this computational study the structural and electronic properties of the 4-hydroxycoumarin and its two 3-substituted derivatives were investigated and used to predict their relative stability and reactivity.

METHODOLOGY

Density function theory (DFT) study

In order to explore the theoretical-experimental consistency, quantum chemical calculations were performed with complete geometry optimizations using standard Spartan 10 software. Geometry optimization was carried out by B3LYP/6-31G* level of theory. The chemical reactivity descriptors calculated using DFT are: total energy (E), chemical hardness (η), electronic chemical potential (μ) and electrophilicity (ω).

Chemical hardness measures the resistance to change in the electron distribution or charge transfer and it associates with the stability and reactivity of a chemical system. On the basis of frontier molecular orbitals, chemical hardness corresponds to the gap between the HOMO and LUMO. Chemical hardness is approximated using equation 1 (Peters, Lanzilotta, Lemon, et al., 1998).

$$\eta = (E_{\text{LUMO}} - E_{\text{HOMO}})/2 \quad (1)$$

where E_{LUMO} and E_{HOMO} are the LUMO and HOMO energies. Electronic chemical potential is defined as the negative of electronegativity of a molecule and calculated using equation 2.

$$\mu = (E_{\text{LUMO}} + E_{\text{HOMO}})/2 \quad (2)$$

Physically, μ describes the escaping tendency of electrons from an equilibrium system.

Global electrophilicity index (ω), is calculated using the electronic chemical potential and chemical hardness as shown in equation 3.

$$\omega = \mu^2/2\eta \quad (3)$$

This index measures the propensity or capacity of a species to accept electrons. It is a measure of the stabilization in energy after a system accepts additional amount of electronic charge from the environment.

RESULTS AND DISCUSSION

Structural and electronic properties

DFT calculations were performed for coumarin derivatives **1**, **2** and **3**. Optimized molecular structures of the most stable form are shown in Figure 1.

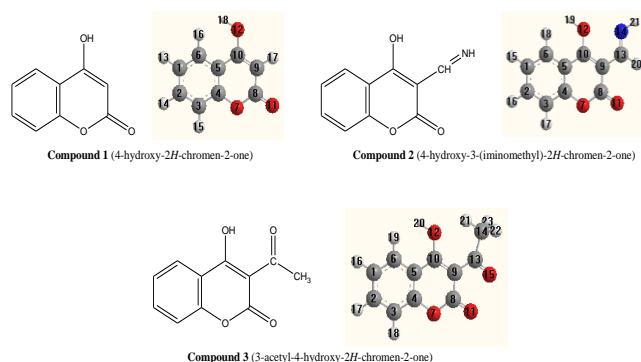


Figure 1. The 2D and 3D structures of coumarin derivatives

Molecular orbital calculations provide a detailed description of orbitals including spatial characteristics, nodal patterns and individual atom contributions. The contour plots of the frontier orbitals for the ground state are shown in Figure 2, including the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO).

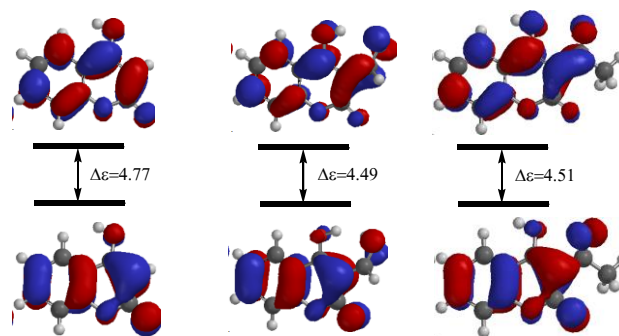


Figure 2. Frontier molecular orbitals of coumarin derivatives

Table 1. Global chemical reactivity indices of coumarin derivatives

	1	2	3
E (au)	-572.26	-665.71	-724.90
E_{HOMO} (eV)	-6.31	-6.48	-6.49
E_{LUMO} (eV)	-1.54	-1.99	-1.98
Dipole moment (debye)	8.18	7.15	8.57
logP	0.92	0.12	0.67
Energy gap (Δ) (eV)	4.77	4.49	4.51
η (eV)	2.38	2.24	2.25
μ (eV)	-3.92	-4.23	-4.23
ω (eV)	3.23	3.99	3.98

It can be seen that the energy gaps between HOMO and LUMO of compound **1** is 4.77, compound **2** is 4.49 and compound **3** is 4.51. The lower value in the HOMO and LUMO energy gap explains the eventual charge transfer interaction taking place within the molecules (Kadhum, Al-Amiery, Musa, et al., 2011). The larger the HOMO–LUMO energy gap, the harder and more stable/less reactive the molecule (Chattaraj, Maiti, 2003; Liu, 2005; Kadhum, et al., 2011).

Table 1 (row 7) contains the computed chemical hardness values for compounds **1**, **2** and **3**. The results indicate that compound **1** is harder and less reactive than compound **3** which is harder and less reactive than compound **2**. The values of μ for compounds **1**, **2** and **3** are presented in Table 1 (row 8). The trend in electronic chemical potential for coumarin derivatives is $2 > 3 > 1$.

The greater the electronic chemical potential, the less stable or more reactive is the compound. Therefore, compound **2** is more reactive than compounds **1** and **3**.

Compound **1** is the least reactive. The electrophilicity values (Table 1, row 9) for the compounds **1**, **2** and **3** are 3.23 eV, 3.99 eV and 3.98 eV. Among the compounds, compound **2** is the strongest electrophile while compound **1** is the strongest nucleophile. A good, more reactive, nucleophile is characterized by a lower value of ω and a good electrophile is characterized by a high value of ω .

Electrostatic potential charges and related quantum chemical properties

The distribution of the electronic density (electrostatic potential charges), related quantum chemical parameters [dipole moment (Table 1, row 4), HOMO/LUMO gap (Table 1, row 6) and the partition coefficients of the compounds (logP; Table 1, row 5)] were calculated for observed coumarines. These values and properties are very useful and can be used in order to evaluate chemical properties and possibilities for interaction of coumarines with biological macromolecules (receptors, enzymes). All these structural, electronic parameters and logP can be also used for a building of quantitative structure-activity relationship (QSAR) model, because all of them are closely related to pharmacokinetics (absorption, distribution, metabolism and excretion) and pharmacodynamics.

CONCLUSIONS

Obtained quantum-chemical calculations correlate well with experimental research related to coumarin compounds. Reaction mechanisms involving these compounds as precursors for many synthetic routes are highly explainable by this computational method and given results. These calculations were once more proof that by means of mathematical models it is possible to describe chemical interactions and simulate the behavior of chemical systems – molecules and reactions.

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Summary/Sažetak

Za tri sintetizirana kumarinska derivata ispitana su njihova kvantno-hemijska svojstva. Ispitivani spojevi polazne su komponente u mnogim reakcijama dobijanja biološki aktivnih spojeva.

U svrhu istraživanja teoretsko-eksperimentalne dosljednosti, DFT deskriptori globalne hemijske reaktivnosti (hemijska tvrdoća, totalna energija, elektronski hemijski potencijal i elektrofilnost) za ove supstance su izračunati koristeći standardni Spartan 10 program. Kompletna geometrijska optimizacija je urađena na B3LYP/6-31G* teorijskom nivou.

Neke kvantno-hemijske kalkulacije se dobro slažu s eksperimentalnim istraživanjima na ovim spojevima. Mehanizmi reakcija u kojima su ovi spojevi početni reaktanti mogu se djelimično objasniti rezultatima ovih proračuna.

Ovo izračunavanje je još jedan u nizu dokaza da je pomoću matematičkih modela moguće opisati hemijske interakcije i simulirati ponašanje hemijskih sistema – molekula i reakcija.