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New Coumarin Ring-Containing Ester Molecule: Facile Synthesis, Characterization, Computational Studies and SwissADME Prediction

Kamuran SARAÇ[1*]

[1]*Bitlis Eren University, Faculty of Science and Arts, Department of Chemistry, Bitlis, Turkey*

(ORCID: 0000-0001-6684-8969)

Keywords: 4-Coumarinyl-2-methyl benzoate, Reaction Mechanism, Swissadme, Quantum Chemistry

Abstract

The aim of the study was to synthesize 4-Coumarinyl-2-methylbenzoate, elucidate the reaction mechanism, perform quantum chemical calculations, and examine the swiss adme properties of the compound. 4-Coumarinyl-2-methylbenzoate compound was synthesized by nucleophilic substitution reaction. The compound 4-coumarinyl 2-methyl benzoate has been characterized both experimentally and theoretically using quantum chemical calculations and spectral techniques. Nuclear magnetic resonances and infrared spectroscopic values of ^{1}H and ^{13}C in the ground state of the compound were calculated both experimentally and theoretically (density functional theory method was used when making theoretical calculations). It was observed that the calculated infrared and nuclear magnetic resonance values were compatible with the experimental values. The energy difference between the HOMO-LUMO of the 4-Coumarinyl-2-methylbenzoate compound was calculated and it was found that this difference was 1.409 Ev. Finally, swiss adme properties of 4-Coumarinyl-2-methylbenzoate compound such as Molecular Mass (Size), Flexibility (FLEX), Polarity, Saturation (Insatu), Lipophilia, Water Solubility were examined.

1. Introduction

Coumarins are the general name given to a group of chemical compounds naturally found in plants and known for their pleasant odors. Coumarins are found especially in cinnamon, blueberries, oak and some other plants [1]. These compounds play a role in the scents of plants and, in some cases, their defense mechanisms. Due to the distinctive odor of coumarins, they are widely used in the perfumery and cosmetics industry. However, it is known that coumarins can be toxic in high doses. For this reason, the use of coumarin-containing products is limited or regulated in some countries [2]. Coumarins are also used in the pharmaceutical industry. For example, coumarin derivatives, which are anticoagulant drugs, significant in the field of medicine [3]. However, the use of coumarin derivatives is carefully monitored because there is a need to control side effects and dosage [4]. Since coumarin derivatives are used in such a wide and diverse field, for the first time in this study, with the aim of using them in at least one of these areas, 4-Coumarinyl-2-methylbenzoate, which is formed by the nucleophilic addition and dissociation reaction of 4-Hydroxycoumarin and 2-methylbenzoyl chloride aroyl compounds, has been investigated. It is aimed at experimental as well as quantum chemical calculation.

2. Material and Method

2.1. Experimental

Synthesis of 4-Coumarinyl-2-methylbenzoate (III)

2-methylbenzoyl chloride (II) (10 mmol) was added dropwise to the solution containing 4-hydroxycoumarin (I) (10 mmol) and pyridine (25 mmol) and mixed for 30-40 minutes at room temperature. The resulting mixture was added to ice water containing dilute hydrochloric acid. After the

*Corresponding author: ksarac@beu.edu.tr
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substance was washed with water and filtered, it was placed in 100 mL solution containing 5% sodium bicarbonate and mixed thoroughly. After the product in the beaker was filtered, it was left to dry in the open air. The dried substance was crystallized in ethanol. Yield:(1,9g) 76%, m.p: 135-137° C, ^{1}H-NMR: 2.45 (s,3H) CH_3; 6,60 (s, 1H) (C-3); 7,20-8,20 (m,8H) phenyl (coumarin and benzoyl). ^{13}C-NMR: δ 116-135 phenyl (coumarin and benzoyl). FT-IR (KBr, cm^{-1}, υ): 1742 cm^{-1} (C=O lactone), 1712 cm^{-1} (C=O ester), 1130 cm^{-1} (C-O)

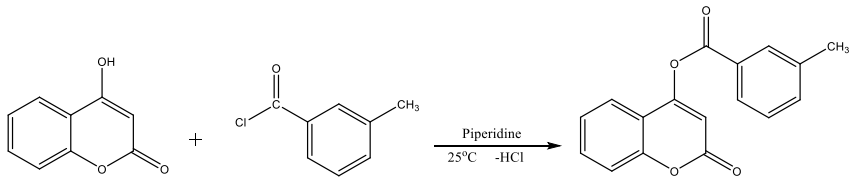

Figure 1. Synthesis of title compound.

2.2. Computational methods

All theoretical calculations in this work were computed with Gaussian 09 software **[5]**. The 4-Coumarinyl-2-methylbenzoate was optimized by the B3LYP with 6-311G(d,p) basis set. Theoretical ^{1}H and ^{13}C of NMR values were computed within the Gauge Independent Atomic Orbitals (GIAO) approach. The harmonic vibrational frequencies for the optimized structure were assessed and the theoretically obtained frequency values were scaled by 0.958[6].

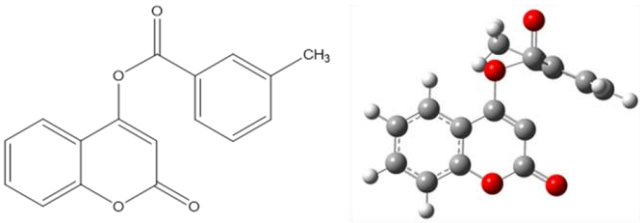

Figure 2. (a) Experimental structure of the compound (b) Optimized structure of the compound by B3LYP/6-311G(d,p) method.

3. Results and Discussion

3.1. Analysis of the synthesized $C_{17}H_{12}O_4$ (III) molecule

The 4-hydroxycoumarin was produced through the nucleophilic addition dissociation reaction of 2-methylbenzoyl chloride and aroyl compounds, and forms 4-Coumarinyl 2-methylbenzoate with a good yield (76%). The reaction formation mechanism of the compound is given in figure 3. As seen in Figure 3 the unshared electron pairs on the oxygen carry out nucleophilic addition to the carbonyl carbon in the acyl structure, the part of which is in the positive state. Then, since the chlorine atom has a high electronegativity, the reaction is completed by separating one mole of hydrochloric acid (-HCl) from the structure.

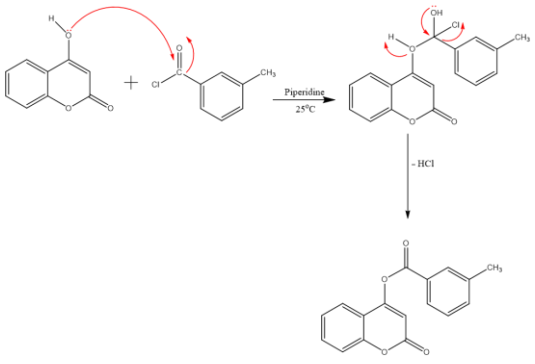

Figure 2. Formation mechanism of 4-Coumarinyl 2-methyl benzoate

3.2. FT-IR and NMR analysis

While there is a peak of hydroxide (OH) tension in the 3200-3600 cm^{-1} range in the 4-hydroxycoumarin structure, this peak disappears in the compound formed as a result of the reaction and is replaced by carbonyl (C=O), which indicates ester formation, theoretically 1776 cm^{-1}, experimentally 1773 cm^{-1}) stress peaks appear [7]. On the other hand, asymmetric aliphatic stretching peaks at 2848 cm^{-1} and symmetrical aliphatic stretching peaks at 2780 cm^{-1}, coming from the methyl substituent, and CH_3 in-plane bending peaks at 1464 cm^{-1} and CH_3 out-of-plane bending peaks at 1042 cm^{-1} were observed [8], [9]. Additionally, evaluations of other experimental and theoretical FT-IR spectra of the title compound molecule are given in detail in Table 1.

Table 1. Comparison of 4-Coumarinyl-2-methylbenzoate vibration frequencies

Symbols		Calculated B3LYP/6-311G(d,p)	Experimental FT-IR(cm^{-1})
υ	CH, Ar	2991	3010
υ	CH, Ar	2969	-
υ_{as}	CH, Ar	2965	-
υ	CH, Prn	2957	2970
υ_{as}	CH, Ar	2948	-
υ_{as}	CH, Ar	2946	-
υ	CH, Ar	2944	2958
υ_{as}	CH_3	2848	-
υ_{as}	CH,CH_3	2841	-
υ_{s}	CH_3	2780	-
υ	CH, Ar+ υs CH_3	2774	-
υ	C=O+ υC=C	1776	1773
υ	C=O, Prn	1737	1712
υ	C=C, Ar	1599	1606
δ	C-H	1590	-
υ	C=C, Ar	1578	1568
δ	C-H	1475	1488
δ	CH_3	1464	-
δ	CH	1446	1449
α	CH_3	1399	1409
α	CH, Ar	1293	1298
υ	C-C + α CH, Prn	1246	-
υ	C-O,Prn + α CH, Ar	1233	1208
α	CH, Ar	1123	1130
α	CH_3	1042	1033
υ	C-O Prn + C-C	971	956
α	CH, Ar	845	835

υ, stress; δ, in-plane bending; α, out-of-plane bending;
Ar, aromatic; prn, pyron; s, symmetric; as, asymmetric;

When the ^{1}H-NMR chemical shift values of the compound were compared, it was seen that the chemical shift peaks of Hydrogen atoms bonded to electropositive atoms were small. The most characteristic peaks in the synthesized 4-Coumarinyl 2-methylbenzoate compound are the protons of methyl (CH_3), which were observed experimentally at 2.45 and theoretically as singlets at 2.52 ppm.

On the other hand, when the ^{13}C-NMR chemical shift values were examined, it was seen that the carbon atoms of the Phenyl (Benzoyl) ring resonated at high fields due to the increase in electron density on the atoms adjacent to the electropositive atoms, and their chemical shift values were small.

Additionally, evaluations of the experimental and theoretical ^{1}H-NMR and ^{13}C-NMR spectra of the compound calculated using the same method are given in Table 2.

Table 2. Experimental and calculated NMR spectrum values of 4-Coumarinyl-2-Methyl Benzoate

Atom	Experimental (ppm) (DMSO-d_6)	Calculated (ppm) B3LYP/6-311G(d,p)
C (Coumarin and Bezoyl)	115-134	108-142
3H (CH_3)	2.46	2.54
1H (C-9)	6.63	7.85
8H (Coumarin and benzoyl)	7.20-8.20	7.01-8.18

3.3. Frontier Molecular Orbitals (FMO) and Electronic Properties

HOMO: This is the highest energy orbital that contains electrons. Electrons in the HOMO are involved in chemical bonding and are more likely to participate in chemical reactions. LUMO: This is the lowest energy orbital that is unoccupied [10]. It's important because it represents an energy level to which electrons can be excited during a chemical reaction. The energy difference between the HOMO and LUMO, often referred to as the HOMO-LUMO gap, is a crucial parameter in understanding various properties of molecules, especially their reactivity and optical properties. Molecules with smaller HOMO-LUMO gaps tend to be more reactive and have different colors compared to those with larger gaps[11], [12].

The molecule was calculated in the DFT/B3LYP/6-311G(d,p) set, and its HOMO and LUMO orbitals are given in Figure 4. As can be seen from the figure, the energy difference between the HOMO and LUMO of the compound is 1.409 eV. This energy gap indicates that the molecule is not in a very stable structure.

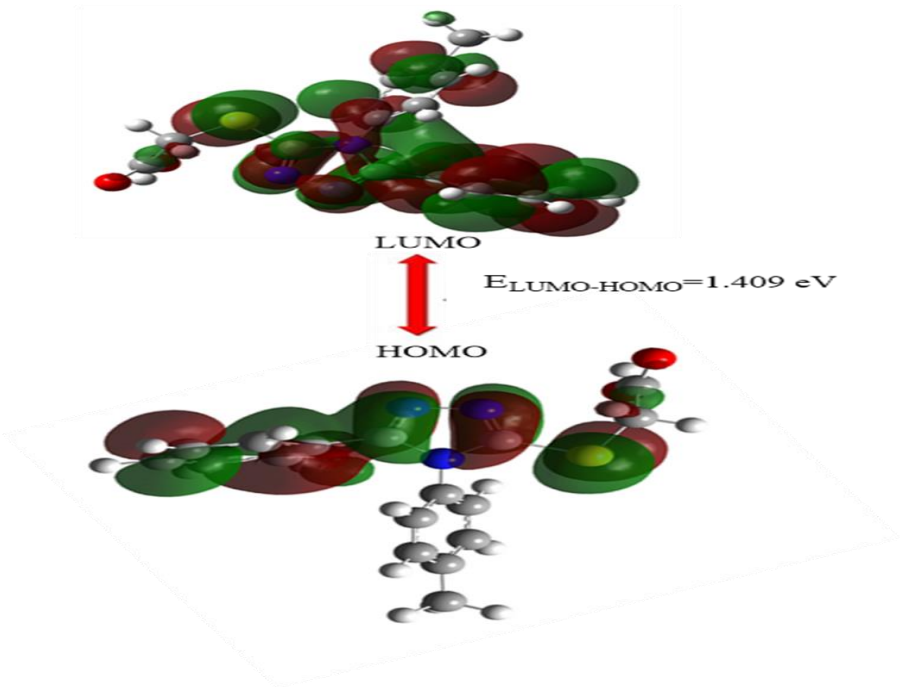

Figure 4. By method B3LYP/6-311G(d,p) of the title compound calculated HOMO and LUMO energies.

3.4. Swiss Adme Properties

It is one of the widely used tools to estimate the absorption, distribution (Absorption and Distribution of Drugs in the Body), biotransformation and excretion (Metabolism (Biotransformation) Excretion of Drugs in the Body) of drugs in the body in silico

and how to estimate some of the pharmacokinetic properties of these parameters and molecules. Traditionally, therapeutics are small molecules that fall under Lipinski's rules. These rules are as follows[13].

1: Molecular Mass (Size): The mole weight of the molecule must be between 150 and 500 g/mol^{-1}. Accordingly, the molar weight of the synthesized compound is 280.27 g/mol^{-1}.

2: Flexibility (FLEX): A rotatable bond is defined as any single non-ring bond bonded to a non-terminal, non-hydrogen atom (No more than nine rotatable bonds): the title compound number there are 3 types of rotatable bonds.

3: Polarity: The polar surface area (PSA) or topological polar surface area (TPSA) of a molecule is defined as the surface sum of all polar atoms or molecules, especially oxygen and nitrogen, as well as the hydrogen atoms attached to them. (TPSA between 20 and 130 Å), the title compound TPSA: 56.51 Å^2

4:Saturation (Insatu): Saturation, carbon fraction in sp^3 hybridization is not less than 0.25; Fraction of the compound Csp^3=0.06.

5: Lipophilia or Lipophilism: Lipophilicity refers to the ability of a chemical compound to dissolve in oils, lipids and non-polar solvents such as hexane or toluene. Such nonpolar solvents are lipophilic. LogP is a key component of Lipinski's Rule of five recommendations, which predict the drug-likeness of a new synthetic compound. According to Lipinski's Rule of Five, for good oral and intestinal absorption of an oral drug, the LogP value should be <5, ideally between 1.35-1.8. The LogP value of the compound is: 2.79.

6:Water Solubility: All estimated values are the decimal logarithm of the molar solubility in water (log S). Compounds can be classified according to their solubility values (LogS); Compounds with solubility values of 0 and higher are highly soluble, those in the range of 0 to -2 are soluble, those in the range of -2 to -4 are slightly soluble, and those in the range of -4 are insoluble. LogS value of the compound: -4.09.[14], [15], [16].

According to these data, as seen in Figure-5, the compound largely meets the swissadme properties.

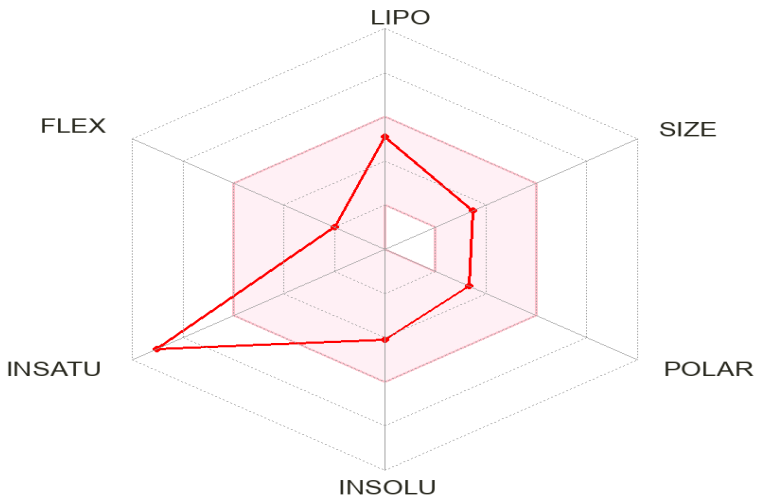

Figure 5. Bioavailability radar for title compound within the domain borders of ADME properties, calculated by SwissADME

4. Conclusion and Suggestions

In this study, nucleophilic addition-dissociation reaction was carried out with 4-Hydroxycoumarin and 2-methylbenzoyl chloride, and 4-coumarinyl 2-methylbenzoate compound was obtained in good yield. From the experimental values of the obtained compound and the NMR and infrared spectrum results calculated using the DFT/B3LYP/6-311G(d,p) basis set, it was observed that the vibration types of some characteristic peaks were compatible with both the literature values and each other. In addition, the energy difference between the HOMO and LUMO frontier orbitals of the compound was calculated as 1.409 eV, and this large energy gap shows that the molecule is not very stable. Finally, the siwiss adme

properties (Molecular Mass, Flexibility, Polarity, Saturation, Lipophilia or Lipophilism, Water Solubility) of the compound were examined and according to the data obtained, it was seen that the compound largely met the siwiss adme properties.

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Statement of Research and Publication Ethics

The study is complied with research and publication ethic

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