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Structural characterization of derivatives of 4-methylcoumarin – Theoretical and experimental studies

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HIGHLIGHTS

- 4-Methylcoumarins are structurally investigated using theoretical and experimental methods.
- Coumarin fragment is nearly planar.
- Substituted acetyl and methoxy groups are coplanar or orthogonal to benzopyrane ring.
- π···π Interactions stabilize supramolecular architecture of crystals of 4-methylcoumarins.

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ABSTRACT

The quantum chemical conformational analysis was performed for 4-methylcoumarin derivatives substituted with the hydroxy, acetyl and/or alkoxy groups. Their crystal structures were determined by a single crystal X-ray crystallography. The structural data in the solid were compared with the results of the quantum chemical analysis in the gas phase. The results indicated that the coumarin system is nearly planar and several conformers differing in the orientation of the methoxy and acetyl groups are observed. The stereochemistry of the lowest energy rotamers in the gas phase is retained in solid state; intermolecular forces are to weak for inducing conformational changes. In the crystals of studied 4-methylcoumarin derivatives the π···π stacking of benzopyran systems is a very characteristic and persistent feature of the molecular association. The extend of the π···π overlapping depends on substituents.

1. Introduction

The coumarin and its derivatives occur naturally in plants. They show therapeutic effects and have been used in the folk medicine as the traditional remedies [1–4]. The natural as well as synthetic coumarin derivatives, therein 4-methylcoumarins, have a large spectrum of biological activity, viz. they possess anti-inflammatory, antioxidant, antithrombotic, antiviral and anticarcinogenic activities [5–9]. Simple coumarins vary considerably in their molecular structure and this influence their pharmaceutical properties [6–9]. The mode and strength of their activity usually could be modified by the number and type of small substituent, namely hydroxy or methoxy groups. Depending on the substitution pattern, simple coumarins can be divided into: hydroxycoumarins (e.g. warfarin, umbelliferone, aesculetin, aesculin, dicoumarol), methoxycoumarins (e.g. herniarin, scoparon) and hydroxymethoxycoumarins (e.g. scopoletin, scopolin, fraxetin, fraxin, fraxidin, isofraxidin). In the therapeutic application, the most important natural derivative of coumarin is dihydroxycumarin. This compound gave rise to the synthesis of a series of anticoagulant drugs such as dicumarol [10], sintrom, marcumar and coumadin [11]. Many of these agents are bound to serum proteins, especially human serum albumin (HSA). This binding affects their pharmacological and pharmacokinetical properties. The alkylcoumarins bind to the domain II of HSA [12], whereas warfarin (coumadin) and analogous anticoagulants (hydroxycoumarins) bind to the domain II and site-1 of HSA [13]. The coumarins are present in the group of anti-HIV [9,14,15] and antibacterial agents (e.g. novobiocin) [16].

The structural studies of complexes formed by simple coumarins with diverse proteins indicated that the nature of ligand–protein binding is a combination of hydrophobic, electrostatic and/or

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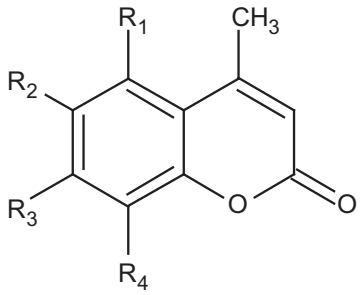


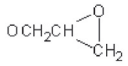
	R_1	R_2	R_3	R_4
1	OH	C(=O)CH_3	CH_3	H
2	OH	OH	OCH_3	H
3	H	H	OCH_3	C(=O)CH_3
4	H	OCH_3	OCH_3	

Fig. 1. Molecular formulae of the investigated compounds 1–4.

hydrogen bonding interactions. The intermolecular forces binding coumarins to the active site include the π-stacking and O–H···O hydrogen bonds (see Supplementary Material). Precisely, the π···π stacking of benzopyran fragment with phenyl rings of phenylalanine or thyrosine [17–19], and the O–H···O hydrogen bonds between hydroxycoumarins and amino acids (viz. serine, aspartic and glutamic acid residues) [14,20,21] are observed.

Moreover, a common arrangement of molecules of 4-methylcoumarin derivatives in their crystals is the π···π stacking (see Supplementary Material). The range of the overlapping of parallel benzopyran fragments could be modified by the substituents. Among 20 selected crystals of this group, only the molecules of 7-hydroxy-4-methylcoumarin have non-stacking arrangement [22], while even crystals of hydrates pack in the typical parallel mode of aromatic moieties [23–26].

The specific role of the methyl substituents attached to the coumarin system is observed. These groups modify e.g. antimutagenic [27] and antioxidant [28,29] activity of coumarin. In general, the toxicity of coumarin is reduced by its substitution with one or more methyl groups and 4-methyl derivatives are known to be less toxic than the other coumarins [28–30]. Therefore, in this work, we present the conformational analysis of 4-methylcoumarin derivatives with the hydroxy, alkoxy and/or acetyl groups substituted to the benzene ring, viz. 6-acetyl-5-hydroxy-4,7-dimethylcoumarin (**1**), 5,6-dihydroxy-7-methoxy-4-methylcoumarin (**2**), 8-acetyl-7-methoxy-4-methylcoumarin (**3**) and 6,7-dimethoxy-4-methyl-8-(oksiran-2-ylmethoxy)coumarin (**4**) (Fig. 1). Their molecular structure in gas phase and solid will be discussed. In particular, the orientation of substituents attached to the coumarin ring system will be analyzed in details. Moreover, the intermolecular association mode in the crystals of compounds **1–4** will be presented.

2. Experimental

2.1. Synthesis

The compounds **1–4** were synthesized according to the previously published methods [31–34]. The chemicals were obtained from Sigma–Aldrich and used without further purification. Single crystals suitable for an X-ray diffraction were prepared by a slow evaporation of the solvent from an ethanolic solution at room temperature.

2.2. Computational details

The calculations were performed using the Gaussian03 program package [35]. The geometry of the molecules **1–4** in the gas phase was optimized with B3LYP [36,37] exchange–correlation potential, using a standard 6-31G(d) [38] basis set. The atomic coordinates found in the solid state were used as the initial guess. The PES scan study has been performed for **1–4**. The scans started from the zero value of the torsion angle up to ±180° with a step of 10°. The geometry of the conformers corresponding to the minima on the PES was optimized with the B3LYP method using the 6-31++G(d,p) basis set. The vibrational frequency calculations were performed for the found conformers and all frequencies were real.

2.3. X-ray crystallography

The diffraction data for the crystals of **1–4** were collected on an Oxford Diffraction KM4 or Xcalibur diffractometer. The structure was solved by direct methods using the SHELXS-97 program and refined by the full-matrix least-squares method on F^2 using the SHELXL-97 program [39]. The non-hydrogen atoms were refined with anisotropic displacement parameters. The C-bonded H-atoms were positioned geometrically and allowed to ride on the attached atom. The primary positions of the O-bonded H-atoms were taken from the difference electron-density maps. The crystal data, details of the data collection and refinement are given in Table 1.

CCDC 903645, 903646, 903647, and 903648 contain the supplementary crystallographic data for compounds **1–4**, respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: data_request@ccdc.cam.ac.uk.

3. Results

3.1. Conformational analysis in gas phase

The molecules of studied coumarins have the substituents, such as hydroxy, acetyl and/or alkoxy groups, attached to the planar aromatic system (Ar). Since the 4-methylcoumarin fragment is rigid, the potential energy surface (PES) for the internal rotation about the $\mathbf{C}_{Ar}$—$\mathbf{C}$(=O)CH_3 and $\mathbf{C}_{Ar}$—$\mathbf{O}CH_3$ single bonds in the molecules **1–4** has been explored using the quantum-chemical methods. The DFT calculations yielded several conformers shown in Fig. 2.

For **1** and **2**, only one stable form is observed, in which the acetyl (**1.1**) or methoxy (**2.1**) groups are coplanar to the coumarin moiety (Table 2).

Three stable conformers are observed for the molecule **3**, viz. **3.1**, **3.2** and **3.3** (Fig. 2), the energy difference between them is less than 2 kcal/mol. All of them have similar orientation of the acetyl substituent (Table 2). However, the methoxy group is able to adopt two orientations with respect to the aromatic ring: coplanar (**3.1** and **3.2**) and perpendicular (**3.3**). The C12—O3—C7—C6 fragment is synplanar for the conformer **3.1** and antiplanar for **3.2** (Fig. 2).

The rotation about $\mathbf{C}_{Ar}$—$\mathbf{O}CH_3$ bond for both methoxy groups of the molecule **4**, being in the *ortho* position, yields three stable forms **4.1–4.3** (Fig. 2). The most stable conformer **4.1** has the —OCH_3 substituent at the C6 position coplanar and the —OCH_3 at the C7 atom perpendicular to the aromatic system. Moreover, the *trans* and *cis* orientations of the C6/C7—OCH_3 single bonds are observed for the conformers **4.2** and **4.3**, respectively (Fig. 2, Table 2).