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Theoretical and experimental study of a novel psolaren derivate: (E)-9-(3,4-dimethylpent-2-enyloxy)-7H-furo[3,2-g]chromen-7-one
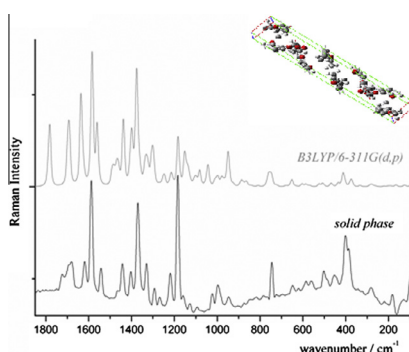
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HIGHLIGHTS

- Specimen *Trichocline reptans*.
- Infrared and Raman spectra.
- X-ray diffraction methods.

GRAPHICAL ABSTRACT

A novel psolaren derivate (E)-9-(3,4-dimethylpent-2-enyloxy)-7H-furo[3,2-g]chromen-7-one, named 8-IOP, which has been recently isolated and chemically characterized. The molecular structure has been studied experimentally by X-ray diffraction methods and theoretically calculations. In addition, the UV/VIS, Raman and infrared spectra were measured for the substance and the vibrational wavenumbers calculated by quantum chemistry procedures.

ABSTRACT

A new psolaren derivate, (E)-9-(3,4-dimethylpent-2-enyloxy)-7H-furo[3,2-g]chromen-7-one, has been isolated and characterized by experimental and theoretical methodologies. The solid state molecular structure has been determined by X-ray diffraction methods. The substance crystallizes in the monoclinic P2₁/c space group with $a = 4.2389(5)$, $b = 26.090(3)$, $c = 12.482(1)$ Å, $\beta = 96.990(9)°$, and $Z = 4$ molecules per unit cell. The crystal structure shows the molecule fused phenyl and hetero-cycle rings to be coplanar with each other. Ab initio(MP2) and DFT methods have been used to predict the molecular structure in the isolated molecule approximation and the results compared with the experimental data. The MP2/6-311G(d,p) calculations are in good agreement with the X-ray results. The calculated HOMO–LUMO energy gap shows that the intra-molecular charge transfer could easily occur, a prediction closely related to the observed bioactivity of this new compound. In addition, the infrared absorption and Raman dispersion spectra were recorded and an assignment of the observed spectral features to molecular vibrations was made. The vibrational study was assisted by quantum chemistry calculations at the MP2 and DFT level, which provided theoretical mode frequencies. The study was completed by natural bond orbital (NBO) analysis.

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Introduction

Coumarins are chemicals found in a large number of natural products. They occur widely as secondary plant metabolites and are known to exhibit numerous biologically relevant properties. More than 1800 different natural coumarins have been already discovered and described. Most of these are mono- or di-hidroxilated at the aromatic ring [1]. Recently considerably attention has been devoted to the less common tri- and tetra-oxygenated coumarins, which have been shown to exhibit several interesting pharmacological properties, including antibacterial [2] anti-platelet aggregation [3] and anti-leukemia activity [4]. Many natural 5,6,7-trioxygenated coumarins possess the ability to induce cell differentiation in human leukemia U-937 cells, an observation that make them a potential key compound in the search for differentiation [5].

The furocoumarins are compounds present in species belonging to the *Umbelliferae, Rutaceae, Moraceae, Rosaceae, Leguminosae* and some *Asteraceae* families. Furocoumarins are also referred to as psoralens. They are produced by many plants in response to stresses such as bruising or injury caused by predation. The plants respond to damage by enhancing natural pesticide production to prevent insect attack or fungal infection.

These naturally-occurring furocoumarins have been used clinically, coupled with ultraviolet light, to treat dermatological disorders for more than 200 years. They are known to posses photo-sensitizing properties and have been used extensively in photo-chemotherapy [6].

In spite of having different biological functions, psoralens have similar molecular structures. Thus it is very important, from a chemical point of view, to characterize those similar chemicals for both scientific and medical research [7].

In this work we present an experimental and theoretical study of a novel psolaren derivate (E)-9-(3,4-dimethylpent-2-enyloxy)-7H-furo[3,2-g]chromen-7-one (for short,8-IOP) which has been recently isolated and chemically characterized. The molecular structure has been studied experimentally by X-ray diffraction methods and theoretically through second-order Moller–Plesset perturbation theory and Density Functional Theory (DFT) methods by using 6-31G(d,p) and 6-311G(d,p) basis sets. In addition, the Raman and infrared spectra were measured for the substance and the vibrational wavenumbers calculated by quantum chemistry procedures. The study was completed with a natural bond orbital (NBO) analysis.

Experimental

Plant material

Specimens of *Trichocline reptans*, *Asteraceae* family, were collected at El Maray (3300 m above sea level), located in Salta Province, Argentina, during January 2009.

Air-dried aerial parts (1500 g) of *T. reptans* were extracted with CH_2Cl_2 (2 × 3 L) at room temperature for 3 days. The extract was evaporated at reduced pressure and mild temperature (40 °C) to give 141.25 g of a crude extract which was then suspended in EtOH at 60 °C, diluted with H_2O and extracted successively with n-hexane and CH_2Cl_2. Evaporation of the CH_2Cl_2 extracts at reduced pressure gave 30.32 g of a residue and a portion of it (10 g) was subjected to Si gel CC (Merck, 70–230 mesh) using CH_2Cl_2 with increasing amounts of EtOAc (0–100%). Then 190 fractions were collected, monitored by thin layer chromatography (TLC) and grouped according to their profile.

Fractions 6–8 (1.9 g) were combined and re-chromatographed over Si gel (230–400 mesh) using CH_2Cl_2 with increasing amounts of EtOAc (0–100%) followed by the collection of 17 fractions. Fraction 7 (CH_2Cl_2-AcOEt 90–10) was processed by high performance liquid chromatography (HPLC) (Beckman ultrasphere C 18 column, 10 mm i.d. × 250 mm, MeOH—H_2O 4:3, 1.5 ml min^{-1}) giving 12.6 mg of crystalline solid: (E)-9-(3,4-dimethylpent-2-enyloxy)-7H-furo[3,2-g]chromen-7-one) (8-IOP) (Rt 7.56 min) (Fig. S1 of Supporting Information).

X-ray diffraction data

The measurements were performed on an Oxford Xcalibur Gemini, Eos CCD diffractometer with graphite-monochromated Cu Kα (l = 1.54178 Å) radiation. X-ray diffraction intensities were collected (w scans with J and κ-offsets), integrated and scaled with CrysAlisPro [8] suite of programs. The unit cell parameters were obtained by least-squares refinement (based on the angular settings for all collected reflections with intensities larger than seven times the standard deviation of measurement errors) using CrysAlisPro. Data were corrected empirically for absorption employing the multi-scan method implemented in CrysAlisPro. The crystal diffracted poorly and only about 42% of the collected intensities up to 0.82 Å resolution was above two standard deviations of experimental errors. The structure was solved by direct methods with SHELXS-97 [9] and the molecular model refined by full-matrix least-squares procedure on *F2* with SHELXL-97 [10]. The terminal isopropyl —$CH(CH_3)_2$ group showed appreciable librational disorder that lead to observed C—CH_3 bond length shortening. Therefore these methyl carbons were refined as a rigid group which was allowed to rotate around the C—$CH(CH_3)_2$ bond.

All hydrogen atoms but the ones of the isopropyl methyl groups (not included in the final molecular model) were positioned stereochemically and refined with the riding model. The locations of the other methyl hydrogen atoms were optimized during the refinement by treating them as rigid groups allowed to rotate around the corresponding C—C bond such as to maximize the residual electron density at the calculated positions. Crystallographic data for the structure reported in this paper (Table S1of SI) have been deposited with the Cambridge Crystallographic Data Center (CCDC861365). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk)

Vibrational spectroscopy

The infrared absorption spectrum of the solid state substance was recorded in the 4000–400 cm^{-1} range and a resolution of 1 cm^{-1} with a Perkin–Elmer GX1 FTIR instrument. A total of 100 scans were accumulated in each condition. The Raman dispersion spectrum at 2 cm^{-1} resolution was measured on a Thermo Scientific DXR Raman microscope with the exciting line provided by a DXR 532 nm laser. A total of 200 scans were accumulated for each condition. The UV/VIS spectra were collected with a Beckman//DU 7500 spectrometer for methanol solutions with a path length of 1 mm. The infrared, Raman and UV/VIS spectra were analyzed with the OMNIC v.7.2 software provided by the manufacturer.

Computational methods

Calculations were carried out with the Gaussian 03 suite of programs [11]. The geometry of the studied compound was optimized at the MP2 [12] and DFT levels using 6-31G(d,p), and 6-311G(d,p) basis sets. DFT calculations were performed using Becke's three-parameter hybrid exchange functional [13] (B3) combined with both the Lee–Yang-Parr gradient-corrected correlation functional [14] (LYP) and the same basis sets as for the MP2 calculations. All calculations were performed using standard gradient techniques and default convergence criteria. The nature of stationary