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Arbutin: Isolation, X-ray structure and computional studies

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ABSTRACT

Arbutin, an active component originated from *Serratula quinquefolia* for skin-whitening use and treating skin related allergic inflammation, was characterized by microanalysis, FTIR, UV–Vis, multinuclear NMR spectroscopy, and single crystal X-ray diffraction method. The geometries of the studied compound were optimized in singlet states using the density functional theory (DFT) method with B3LYP functional. Electronic spectra were calculated by TDDFT method. In general, the predicted bond lengths and angles are in a good agreement with the values based on the X-ray crystal structure data.

1. Introduction

4-Hydroxyphenyl-β-D-glucopyranoside (**1**) (shortly named arbutin) has received significant attention, as evidence from more than 735 papers published in 1995–2010, which contained the term "arbutin" [Scopus; June 2010]. Surprisingly, there is no single crystal X-ray structure reported so far. Arbutin (**1**) has two anomeric forms, α and β [1]. β-arbutin is naturally founded in plants. α-arbutin is either synthesized using various enzymes [2–4] from acetobromglucose and hydroquinone or from the reaction of β-D-glucose pentaacetate and hydroquinone monobenzyl in the presence of phosphorus oxychloride. The natural products containing arbutin for non-prescription medicine are mainly used to treat urinary tract infection, cystitis, kidney stones, and as a diuretic [5,6]. In the body, arbutin is converted to hydroquinone, which has antimicrobial, astringent, and disinfectant properties [5,7], and is also an inhibitor of melanin formation. The inhibition of proliferation of pathogens by phenolic compounds such as arbutin is attributed to its oxidation potentials, placed at 0.466 and 0.691 V at pH 7.5 and 2.0, respectively [10]. Arbutin is also used in some skin-lightening products, because of its very low cytotoxicity [7–9]. Additionally, arbutin is used as a stabilizer for colour photographic images [6]. It has been isolated from numerous plant sources, such as leaves of bearberry (*Arctostaphylos uva-ursi Spreng.*, *Ericaceae*), pear trees (*Pyrus communis L.*, *Rosaceae*), cowberry (*Vaccinium vitis-idaea L.*, *Ericaceae*), and *Bergenia crassifolia* (*Saxifragaceae*). The leaves of *B. crassifolia* were cited in literature as being one of the richest in arbutin (20–30%) [5]. Arbutin is generally present in plants in combination with methylarbutin, especially plants of the *Ericaceae* family [6].

Herein, we report a full spectroscopic characterization, X-ray analysis of single crystal structures and DFT calculation for arbutin which was isolated and identified from the herb of *Serratula quinquefolia*. In the literature data there are few articles dealing with a strict chemical analysis [11,12], including quantum chemical calculations [13]. The arbutin from *S. quinquefolia* will be the main component of a cosmetic preparation which could be used in melanoderma.

2. Experimental

2.1. General

Arbutin was isolated from the flowering herb of *S. quinquefolia*. The *S. quinquefolia* were cultivated in the Garden of Department of Medicinal and Cosmetic Natural Products of the University of Medicinal Sciences in Poznan (Poland). Aerial parts of the plant were collected in August 2007 from plants at the flowering stage. A voucher specimen (No. 162/89) has been deposited at the above mentioned garden. All organic solvents were of analytical grade and purchased from Aldrich. NMR spectra were obtained with Varian 600 operating at 600.19 MHz (^{1}H–^{13}C NMR cosy) and Bruker

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Avance 400 operating at 400.13 MHz (^{1}H) and 100.5 MHz (^{13}C) at 30 °C; chemical shifts referenced to ext. DSS (^{1}H, ^{13}C); coupling constants are given in Hz. FTIR spectra were recorded on a Nicolet Magna 560 spectrophotometer in the spectral range 4000–400 cm^{-1} with the samples in the form of KBr pellets. Electronic spectra were measured on a spectrophotometer lab. Alliance UV–Vis 8500 in the range 1000–180 nm in acetonitrile solution. Elemental analysis: Perkin-Elmer 2400CHSN/O Analyser.

2.2. Crystal structure determination and refinement

Data for **1** was collected on a KM4 diffractometer by using Sapphire-2 CCD detector. For all measurements graphite-monochromated Mo Kα radiation was used. The crystal was cooled down by a cold dry nitrogen gas stream (Oxford Cryosystems equipment), and the temperature stability was within ±1 K. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 (all data) by using the SHELXTL program package [14]. All non-hydrogen atoms were refined anisotropically. Atomic scattering factors had values incorporated in the computer programs. The H atoms bound to C aromatic atoms were refined using a riding model with C–H = 0.95 Å U_{iso}(H) = 1.2 U_{eq}(C). The remaining H atoms were located from different Fourier map and refined isotropically with U_{iso}(H) = 1.2 U_{eq}(C or O).

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-756242 (**1**). Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

2.3. Isolation

Dried aerial parts of *S. quinquefolia* (250 g) were cut into small pieces and exhaustively extracted with methanol at room temperature. The extract was concentrated under reduced pressure providing a residue (16 g), which was chromatographed on a silica gel (Merck, Art 7733) column. Relevant fractions containing **1** were easily detectable on silica gel TLC plates (Merck, Art. 5553, CH_2Cl_2–MeOH 6:1, R_f = 0.14) after spraying with anisaldehyde reagent followed by heating in the temperature of 105 °C for 3 min. The column was eluted with CH_2Cl_2–MeOH mixture (8:1) and yielded **1** (0.857 g) in the form of long white needles (see Figs. 1 and 2).

1; m.p. = 200.5 °C; ^{1}H NMR (D_2O) δ = 3.55 (m, 4H; H7–H10) 3.76 (dd, J_{HH} = 12.4 Hz, J_{HH} = 5.6 Hz, 1H, H12), 3.93 (dd, J_{HH} = 12.4 Hz, J_{HH} = 2.0 Hz, 1H, H12), 4.99 (d, J_{HH} = 7.6 Hz, 1H, H11), 6.88 (d, J_{HH} = 9.0 Hz, 2H, H6, H2), 7.06 (d, J_{HH} = 9.0 Hz, 2H, H5, H3); ^{13}C{^{1}H} NMR (D_2O) 63.51, 72.40, 75.93, 78.53, 79.00, 104.28, 119.17, 121.39, 153.35, 154.19; E.A. [Found C, 50.28; H, 6.19; $C_{12}H_{16}O_7 \cdot H_2O$ requires C, 49.65; H, 6.25%].

3. Results and discussion

Isolated from dried aerial parts of *S. quinquefolia*, **1** contains a hydroquinone ring, hydroxy group, and a D-glucose fragment which adopts a chair conformation. The crystal form of **1** was crystallised with water in space group P 1 21 1 (No. 4), co-crystallised with MeOH, which was associated through strong H15B···O10 and weak bifurcated O15···H5 and O15···H4 hydrogen bonds. The molecules of 1 are linked by hydrogen bonds (Table 2).

3.1. DFT calculations

The calculations were carried out using Gaussian03 program [15]. The DFT/B3LYP method was used for the geometry optimization of studied molecule [16,17]. The electronic structure determination was made by Generalized Gradient Approximation (GGA) using B3P86 functional. Electronic spectrum was calculated by TDDFT [18] method. The calculations were performed by using polarization functions for all atoms: 6-31G(2d,p) – oxygen, 6-31G** – carbon and 6-31G(d,p) – hydrogen. The PCM solvent model was used in the Gaussian calculations with dichloromethane as the solvent.

3.2. IR

In the studied compound the ν_{O-H} band present maximum at 3552 cm^{-1}. The stretching modes of C–H phenyl fragment in arbutin are visible at 3332 and 3275 cm^{-1}. The marked broad band attributed to hydrogen bonds occurred in solid state sample of the studied compound. The maximum peak at 2910 cm^{-1} is related to stretching mode of alkyl fragments. The bands at 1652 and 1601 cm^{-1} correspond to the stretching vibration of carbon–carbon

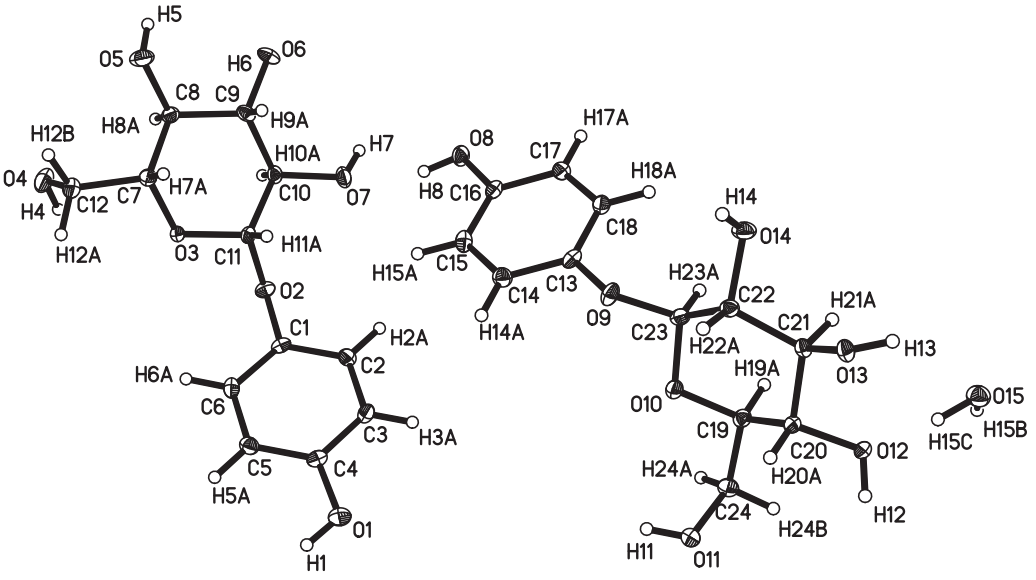

Fig. 1. Molecular structure diagram of **1** (the thermal ellipsoids are drawn at the 50% probability level).