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Structural studies of homoisoflavonoids: NMR spectroscopy, X-ray diffraction, and theoretical calculations

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ABSTRACT

In this article we present a detailed structural investigation for five homoisoflavonoids, molecules important from the pharmacological point of view. For studying the electron distribution as well as its influence on the physicochemical properties, NMR spectroscopy, X-ray diffraction, and theoretical calculations have been used. Nuclear magnetic shieldings obtained by using DFT calculations for optimized molecular geometries are correlated with the experimentally determined chemical shifts. The theoretical data are well in agreement with the experimental values.

The single crystal X-ray structures of homoisoflavonoid derivatives **1**, **3**, and **4** have been solved. The molecular geometries and crystal packing determined by X-ray diffraction are used for characterizing the intermolecular interactions.

Electron distribution is crucial for the stability of radicals and hence the antioxidant efficiency of flavonoid structures. The hydrogen bonding governs the formation of complexes of homoisoflavonoids with biological targets.

1. Introduction

Homoisoflavonoids, derivatives of 3-benzylchrom-4-ones, are constitutionally derived from 1,2-diphenylpropane. They comprise a small family of natural polyphenolics related to flavonoids [1]. Homoisoflavonoids are distributed in many species of the Liliaceae family (*Eucomis bicolor* [1], *Ophiopogon japonicus* [2], *Muscari racemosum* [1,3], *Cremastra appendiculata* [4], and *Veltheimia viridifolia* [5]) and several other plant species (e.g., *Dracaena cinnabari* [3,6] and *Caesalpinia sappan* [7]). They have been shown to possess anti-inflammatory [5], antioxidative [3,6], antiallergic, antihistaminic, and angioprotective activities [4,8] and have been detected as potent phosphodiesterase inhibitors [5]. This report deals with the structure investigation of several homoisoflavonoids, the structures of which are presented in Scheme 1.

For studying the electron distribution as well as its influence on the physicochemical properties, NMR spectroscopy, X-ray diffraction, and theoretical calculations have been performed. Nuclear shieldings obtained by using DFT calculations for optimized molecular geometries are correlated with the experimentally determined chemical shifts. The crystal packing determined by X-ray diffraction is used for characterizing the intermolecular interactions.

2. Experimental

2.1. Compounds

The compounds were prepared according to the published procedures [9,10].

2.2. NMR spectroscopy

The NMR spectra were recorded in $CDCl_3$ using a Bruker Avance 500 NMR spectrometer operating at frequencies of 500.13 MHz (^1H) and 125.77 MHz (^{13}C) and a Bruker Avance 300 NMR spectrometer operating at frequencies of 300.13 MHz (^1H) and 75.48 MHz (^{13}C). All NMR spectra were measured at 303 K. The ^1H NMR chemical shifts were referenced to the residual signal of $C\mathbf{H}Cl_3$ (δ = 7.26 ppm from TMS) and ^{13}C NMR chemical shifts to the signal of the solvent $\mathbf{C}DCl_3$ (δ = 77.00 ppm from TMS). DQF-COSY [11],

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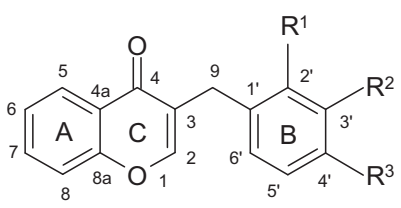

	R^1	R^2	R^3
1	H	OH	H
2	H	H	OH
3	H	H	OMe
4	OMe	H	OMe
5	H	OMe	OMe

Scheme 1. Structures and numbering of the homoisoflavonoid derivatives **1**–**5**.

NOESY (mixing time 800 ms) [12], g-HSQC ($^1J_{H,C}$ = 145 Hz) [13], GSQMBC [14], and g-HMBC ($^nJ_{H,C}$ = 7.5 Hz) [15,16] experiments were further performed in order to reliably assign the chemical shifts. Experimental settings were similar to those published previously [17,18]. Computer processing of the data was performed with Bruker XWINNMR software.

2.3. X-ray crystallography

The X-ray structural data were collected with a KM4CCD four-circle area-detector diffractometer (KUMA Diffraction, Poland) equipped with an Oxford Cryostream Cooler (Oxford Cryosystems, UK). Cell parameters were refined from all the strong (stronger than 1000 pulses) reflections. Data reduction was carried out using the program CrysAlis RED (Oxford Diffraction, UK). Direct methods in SHELXS-97 [19] were used to solve the structures and the structures were refined by using SHELXL-97 [20]. The atomic coordinates and the geometric parameters have been deposited at the Cambridge Crystallographic Data Center (CCDC), Cambridge, UK. The reference numbers are listed in Table 1. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

2.4. Molecular modeling

The molecular frameworks were drawn in HyperChem molecular modeling software [21]. Optimization of the geometries was performed using molecular mechanics (MM+ force field [22,23]). The conformational search for the homoisoflavonoid derivatives was performed utilizing two approaches. In order to locate the possible global energy minimum on the potential energy surface, ten simulated annealing runs in MM+ force field were performed for all of the homoisoflavonoid derivatives **1**–**5**. Each run started from 0 K, followed by 5 ps heating to 300 K in 25 K temperature steps, 10 ps simulation at 300 K, and 5 ps cooling close to 0 K, all in 0.0001 ps time steps. After each run the obtained structures were further optimized using molecular mechanics. In each case the runs led to a single conformer, which was further forwarded for semiempirical AM1 [24] calculation. The AM1 optimized structures were then optimized at B3LYP/6-31G* level of theory using Gaussian03 software [25].

The full conformational space of homoisoflavonoid derivative **1** was systematically investigated. In the first approach torsion angle 1 (C4–C3–C9–C1′) was varied in 30° steps and torsion angle 2 (C3–C9–C1′–C2′) in 90° steps (for numbering of the atoms see Scheme 1). After restraining the torsion angles to the given values in HyperChem software using molecular mechanics, the 48 obtained structures were forwarded for geometry optimizations without restraints applying semiempirical AM1 method of Gaussian03 package. In the second approach for torsion angle 1 values of 30°, 90°, and 150° were given, whereas torsion angle 2 was varied in 60° steps, respectively. The resulting 18 geometries were treated as described above. As a result of these systematic conformational searches, six conformers for homoisoflavonoid derivative **1** were

Table 1
Crystal data and structure refinement for compounds **1**, **3**, and **4**.

Parameter	**1**	**3**	**4**
CCDC Reference No.	763,812	763,813	763,814
Empirical formula	$C_{16}H_{12}O_3$	$C_{17}H_{14}O_3$	$C_{18}H_{16}O_4$
Molecular weight	252.26	266.28	296.31
Temperature (K)	120(2)	120(2)	120(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1/n$	$P2_12_12_1$	$P2_1/n$
a (Å)	7.538(2)	6.2295(6)	6.5111(10)
b (Å)	15.534(3)	12.6396(11)	32.987(4)
c (Å)	10.741(2)	16.5394(15)	6.8996(10)
β (°)	106.86(3)	90	104.856(15)
Volume (Å^3)	1203.7(5)	1302.3(2)	1432.4(3)
Z	4	4	4
Density calc. (Mg m^{-3})	1.392	1.358	1.374
Absorption coefficient (mm^{-1})	0.096	0.093	0.097
F (0 0 0)	528	560	624
Crystal size (mm)	0.60 × 0.50 × 0.20	0.70 × 0.20 × 0.15	0.50 × 0.40 × 0.05
θ range (°)	3.85–25.00	3.45–24.99	3.30–24.98
Index range h	−8 → 8	−7 → 7	−7 → 7
Index range k	−18 → 15	−15 → 13	−39 → 37
Index range l	−11 → 12	−19 → 18	−8 → 7
Reflections collect./unique	5100/2073	7039/2282	8025/2518
Data/restrains/parameters	2073/0/221	2282/0/237	2518/0/201
GOOF	0.981	0.958	1.061
Final R/wR^2 ($I > 2\sigma/I$)	0.0346/0.0822	0.0338/0.0664	0.0494/0.0956
Final R/wR^2 (all data)	0.0455/0.0871	0.0430/0.0698	0.0856/0.1108