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Conformational analysis of 2-hydroxy-2′,5′-diazachalcones

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Abstract

Spatial arrangement of 2-hydroxy-2′,5′-diazachalcones was studied by means of infrared and NMR spectral data and molecular models calculations. The models were calculated in vacuum using semi-empirical AM1 method (software HyperChem 5.1). The initial geometries of the molecules were built by means of standard parameters and then optimized by Polak–Ribiere geometrical optimization. It was found that (*E*)-*s*-*cis*-conformers with synperiplanar arrangement of C-α and C-6 have the lowest heats of formation (ΔH_f°). © 2000 Elsevier Science B.V. All rights reserved.

Keywords: 2-Hydroxy-2′,5′-diazachalcones; Infrared spectra; NMR spectra; Molecular models; Conformational analysis

1. Introduction

Chalcones are an important class of natural compounds. They are precursors in flavonoid biosynthesis and they also play an ecological role in relation to plant colour [1]. Synthetic chalcones and their heterocyclic analogues are most commonly prepared by means of various modifications of the Claisen–Schmidt condensation [2–4]. Another general route involves the Friedel–Crafts acylation of a substituted aromatic compound with a substituted cinnamoyl chloride derivative [2]. Due to the presence of the reactive ketovinylenic group in their molecules chalcones and their analogues exhibit various biological activities, such as antibacterial [5–7], antiviral [8], antiprotozoal [9], antifungal [10,11], anti-inflammatory [2,12], and antineoplastic [13]. The mode of antibacterial action has been suggested to be by the reaction of chalcones with important thiol groups on essential enzymes [5,14]. The diversity of biological actions may render chalcones and their analogues unsuitable as drug candidates because there is a danger of many side effects. However, chalcones are flexible molecules capable of existence in various conformations, and their properties are dependent not only on the presence

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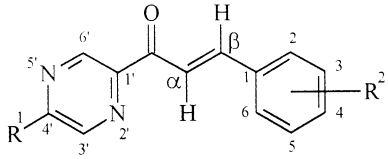
of α, β-unsaturated ketone moiety, but also on a suitable ring substitution. Steric interactions between chalcones and their biological targets are of importance for activity of the compounds [9]. Hence, stabilisation of suitable conformations and introduction of suitable substituents could result in a therapeutically useful agent.

As a part of studies aimed at the synthesis of biologically active pyrazine derivatives a series of ring substituted (*E*)-2′,5′-diazachalcones **1–20** was prepared by condensing acetylpyrazines with aromatic aldehydes in pyridine using diethylamine as the catalyst [15]. Their structures and spectral data are given in Table 1. The compounds exhibited photosynthesis-inhibiting [16], antifungal [17] and antimycobacterial activity [18]. The most pronounced effects were observed with *ortho*-hydroxyl substituted compounds **6–10**. This is in a good agreement with earlier reports pointing out the importance of hydroxyl groups for the antimi-

Table 1
Structures and spectral data of compounds **1–20**[a]



1-20

Compound	R^1	R^2	IR, C = O (ν, cm^{-1})		^{1}H NMR (δ, ppm; J, Hz)		J	^{13}C NMR (δ, ppm)	
			s-Cis	*s-Trans*	H-α	H-β		C-α	C-β
1	H	3-OCH_3; 4-OH	1664	1637	8.00 d, 1-H	7.90 d, 1-H	15.8	116.9	146.4
2	*Tert*-butyl	3-OCH_3; 4-OH	1667	–	8.01 d, 1-H	7.91 d, 1-H	15.8	117.9	145.7
3	Isobutyl	3-OCH_3; 4-OH	1664	–	8.03 d, 1-H	7.91 d, 1-H	15.8	117.7	145.8
4	Butyl	3-OCH_3; 4-OH	1664	1637	8.02 d, 1-H	7.96 d, 1-H	15.8	117.8	145.7
5	Propyl	3-OCH_3; 4-OH	1664	1636	8.00 d, 1-H	7.88 d, 1-H	15.8	117.1	145.8
6	H	2-OH	1665	1636	8.24 d, 1-H	8.31 d, 1-H	16.1	119.5	141.6
7	*Tert*-butyl	2-OH	1652	1630	8.23 d, 1-H	8.34 d, 1-H	16.1	119.9	141.3
8	Isobutyl	2-OH	1652	–	8.24 d, 1-H	8.32 d, 1-H	16.1	119.8	141.3
9	Butyl	2-OH	1661	1637	8.23 d, 1-H	8.31 d, 1-H	16.1	119.8	141.2
10	Propyl	2-OH	1651	–	8.23 d, 1-H	8.30 d, 1-H	16.1	119.8	141.1
11	H	4-OH	1674	1636	8.00 d, 1-H	7.90 d, 1-H	15.9	116.6	146.0
12	*Tert*-butyl	4-OH	1663	1637	8.00 d, 1-H	7.89 d, 1-H	15.9	117.0	145.5
13	Isobutyl	4-OH	1665	–	8.01 d, 1-H	7.88 d, 1-H	15.9	116.9	145.4
14	Butyl	4-OH	1663	–	8.01 d, 1-H	7.89 d, 1-H	15.9	116.9	145.6
15	Propyl	4-OH	1664		8.01 d, 1-H	7.90 d, 1-H	15.9	116.9	145.6
16	H	4-$N(CH_3)_2$	1658	1635	a	a	a	114.5	146.3
17	*Tert*-butyl	4-$N(CH_3)_2$	1651	–	a	a	a	115.0	146.3
18	Isobutyl	4-$N(CH_3)_2$	1656	1636	a	a	a	114.8	146.5
19	Butyl	4-$N(CH_3)_2$	1652	1629	a	a	a	114.9	146.4
20	Propyl	4-$N(CH_3)_2$	1652	–	a	a	a	114.9	146.4

[a] The corresponding protons showed a singlet. In order to investigate solute–solvent interactions, the ^{1}H NMR spectra of compounds **16** and **19** were obtained in $CDCl_3$ after a fifty fold dilution, and gave then the expected AB quartet ($J_{H\text{-}\alpha,H\text{-}\beta} = 15.8$ Hz).

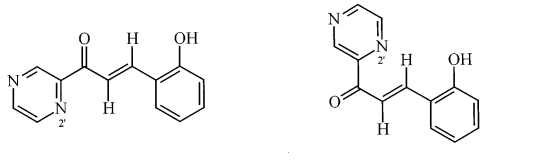


Fig. 1. Possible arrangements of ketovinylenic moiety in the molecule of 2-hydroxy-2′,5′-diazachalcone (**6**) and calculated heats of formation (ΔH_f°) of respective conformers.

crobial action of chalcones [5,10,11]. According to a study concerned with antibacterial properties of chalcones [14], a definite interaction of the receptor with 2- or 3-hydroxyl groups of the (*E*)-chalcones occurs, probably through hydrogen bonding. Lipophilicity studies using RP-TLC showed that 2-hydroxy-2′,5′-diazachalcones **6–10** were more lipophilic than the corresponding 4-hydroxy-2′,5′-diazachalcones **11–15** [19]. However, the increased lipophilicity is probably only one of factors responsible for the higher potency of 2-hydroxy-2′,5′-diazachalcones. Position of the hydroxyl group on the benzene ring and steric arrangement of the molecule may also be of importance. The present study was aimed at finding the most stable conformation of 2-hydroxy-2′,5′-diazachalcones **6–10** on the basis of spectral data and molecular model calculations.

2. Experimental

Infrared spectra were recorded in KBr pellets with an FTIR spectrophotometer Nicolet Impact 400. NMR spectra were recorded at room temperature in $CDCl_3$ in 5-mm tubes using a JOEL GSX-270 (^1H, ^{13}C) FT spectrometer at 270.16 (^1H) and 67.97 (^{13}C) MHz, using the deuterium signal of the solvent as the lock and TMS as internal standard. The parameters were: spectral width 3 kHz (^1H) and 18 kHz (^{13}C), pulse width 3 μs (^1H) and 4.2 μs (^{13}C), acquisition time 5.46 or 0.90 s, number of scans 16 (^1H) and 600 (^{13}C).

Molecular models of possible conformers were calculated in vacuum using semi-empirical AM1 method (software HyperChem 5.1). The initial geometries of the mocules were built by means of standard parameters and then optimized by Polak–Ribiere geometrical optimization, RMS gradient 0.05 kcal $Å^{-1}$ mol^{-1}. Molecular dynamics (with heating to 1200 K) in combination with the manual rotation of single bonds were used for finding the conformer with the lowest energy.

3. Results and discussion

(*E*)-configuration on the vinylenic double bond of the 2′,5′-diazachalcones reported here was confirmed by coupling constant values ($J_{H\text{-}\alpha,H\text{-}\beta}$ = 15.8–16.1 Hz; Table 1).

Carbonyl group can present an *s-cis* or *s-trans* conformation with respect to the vinylenic double bond due to free rotation along the single bond between C-carbonylic and C-α (Fig. 1). A conformational equilibrium between the two conformers is dependent on their structure and the properties of environment, e.g. solvent, temperature [4,20]. According to literature [6,20,21], three bands in infrared spectra are important for determining conformational arrangement of the ketovinylenic system. Infrared spectra of the 2′,5′-dizachalcones reported in the present paper were compared with those reported for similar compounds [6,20,21], and it could be concluded that *s-cis* conformation prevailed in the solid state (KBr pellets). A shoulder at 1636 cm^{-1} was observed in the spectra of several compounds (Table 1). In our opinion, it indicated the presence of a small amount of *s-trans* conformer. Calculated standard heats of formation (ΔH_f°) for 2-hydroxy-2′,5′-diazachalcone **6** (Fig. 1) indicate that (*E*)-*s-cis*-conformer is more stable. Hence, only (*E*)-*s-cis*-arrangement was further considered in computational modeling.

The relative ^1H NMR chemical shift positions of H-α and H-β (on the basis of 2D-Hetero COSY spectra) were reversed for 2-hydroxy-2′,5′-diazachalcones **6–10** compared to that of other compounds (Table 1). From Dreidings models, *ortho*-hydroxyl group shows steric interactions with H-α. The lack of free rotation was also confirmed from NOE experiments. Irradiation of H-α in compound **9** revealed NOE with H-6,

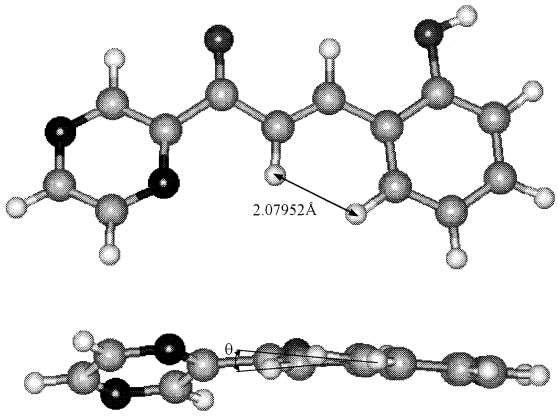


Fig. 2. Optimized model of 2-hydroxy-2′,5′-diazachalcone (**6**).

whilst irradiation of H-α in compound **4** lacking the *ortho*-hydroxyl group gave no observable NOE and irradiation of H-β in the same derivative produced NOEs with both H-2 and H-6. A conformation in which H-α and H-6 are close to each other seemed probable for 2-hydroxy-2′,5′-diazachalcones **6–10** from NOE experiments. This assumption was confirmed from the optimized model of compound **6** where the calculated distance between H-α and H-6 was 2.07952 Å. Torsion angle θ is formed by the plane containing atoms C-α, C-β and C-1 and the plane containing C-β, C-1 and C-6. For the optimized geometry of compound **6** torsion angle $\theta = -10.4287°$ (Fig. 2). The rotation of the phenyl group along the single bond between C-β and C-1 was simulated (in 10° steps) and rotational barriers were calculated. The difference between the conformer with the highest ΔH_f° ($\theta = 100°$) and the conformer with the lowest ΔH_f° ($q = -10°$) was 3.07634 kcal mol^{-1} (Fig. 3). It can be seen from Fig. 3 that conformers with synperiplanar arrangement of C-α and C-6 ($\theta = 0° \pm 30°$) are the most stable ones, whilst antiperiplanar arrangement of C-α and C-6 ($\theta = 180° \pm 30°$) is less favorable, probably due to steric interactions between H-α and *ortho*-hydroxyl group. Conjugated system of double bonds in the cinnamoyl part of the molecule tends to be planar in chalcones and their heterocyclic analogues [22,23]. Therefore, conformers in which phenyl group goes significantly out of co-planarity with α, β-unsaturated ketone moiety have highest heats of formation.

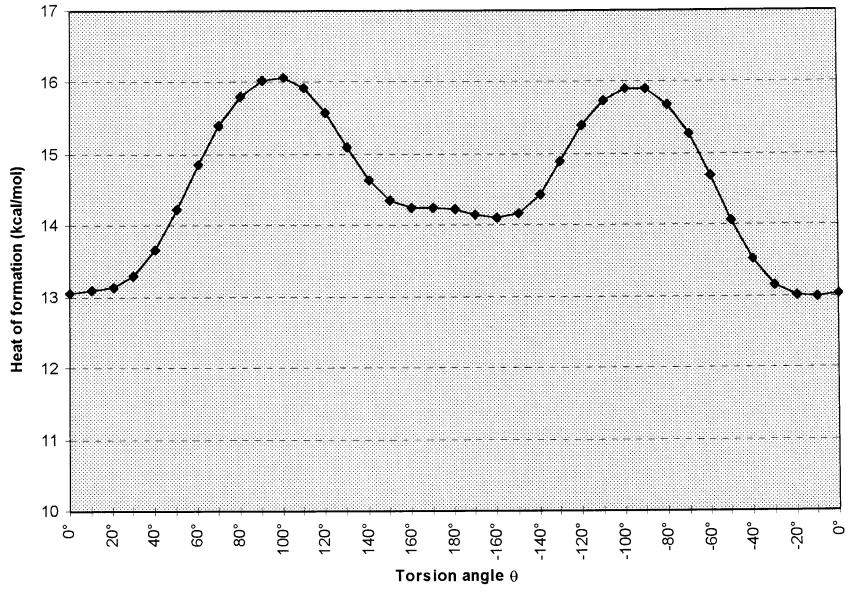


Fig. 3. Relationship between the torsion angle θ and the heats of formation (ΔH_f°) of the corresponding conformers.

Acknowledgements

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