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Cinnamoyl pyrones in proton-donating media: Electronic structure and spectral properties of protolytic forms

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ABSTRACT

Spectral properties of cinnamoyl pyrone (CP) and its derivatives were studied in water–alcohol and water solutions within a wide pH/H_0 range. It was found that the most of CP may exist in neutral, anionic and cationic forms, except for alkylamino substituted CP, which can also form dications. The constants characterizing equilibria between all the protolytic forms were obtained.

CP anions appears as a result of 4-hydroxy group dissociation. It was found that the acidity of CP decreases upon the excitation, that excepts the photodissociation or intramolecular proton transfer in the excited state. The formation of cations and dications occurs by means of protonation of alkylamino group or/and exocyclic carbonyl group.

The theoretical analysis of electronic structure has shown that long-wavelength electronic transitions of neutral and anionic CP forms are of interfragmental charge-transfer (ICT) character. However, in the case of anions, ICT is hindered due to their nonplanar geometrical structure. The band maxima positions in experimental absorption spectra of neutral CP and in absorption and emission spectra of cations correlate linearly with theoretical estimations of charge transfer in CP molecules.

The absence of the fluorescence, characteristic for the most of neutral CP, is due to the intersystem crossing, that is proved by the appearance of the phosphorescence of non-fluorescent CP at low temperatures.

1. Introduction

Cinnamoyl pyrones (CP) (3-[(2E)-3-(4-R-phenyl)-1-oxo-2-propenyl]-4-hydroxy-6-methyl-2H-pyran-2-ones) are structural analogs of 2′-hydroxychalcones, which manifest various aspects of biological activity. It is found that CP and its derivatives have blood-platelet aggregation inhibiting activity [1] and were used as I type collagen gene transcription suppressing agents [2]. Difluoroborate complexes of CP derivatives are known as a novel class of HIV-1 integrase inhibitors [3]. CP can also be used as intermediate products in synthesis of many oxygen and nitrogen containing heterocyclic compounds [4]. Some of them, for example thiazepines [5], are used as apoptosis inducers.

Before, we have obtained several CP derivatives and analyzed peculiarities of their structure [6]. In particular, the tautomerism of CP in the ground state was discussed. In addition, we have investigated the spectral properties of CP neutral forms in aprotic solvents – dichlotomethane and acetonitrile.

However, the CP are used for biological researches in aqueous or alcohol–water solutions, i.e. in protic media, where spectral properties of CP may differ from those in majority of organic solvents. Moreover, in polar media, CP may exist in different acid–base forms possessing different spectral properties and biological activity (CP precursor – dehydroacetic acids exists in neutral aqueous media not only in neutral form, but also in anionic one). That is why, this work was aimed to estimate acid–base properties of CP derivatives in water-containing media and to investigate structures and spectral properties of all the possible protolytic forms of CP.

2. Experimental

CP derivatives (Scheme 1) and 2′-hydroxychalcone have been synthetized and purified according to procedures described before [6,7].

Investigation of CP protolytic forms in the wide pH range (1–12 pH units) was performed in water–methanol 2:8 (v/v) mixtures using NaOH and H_2SO_4 solutions in the same solvent for pH variation. In cases when higher acidities were needed (Hammet acidity function range $H_0 = 1$ to -10), water–sulfuric acid mixtures were used.

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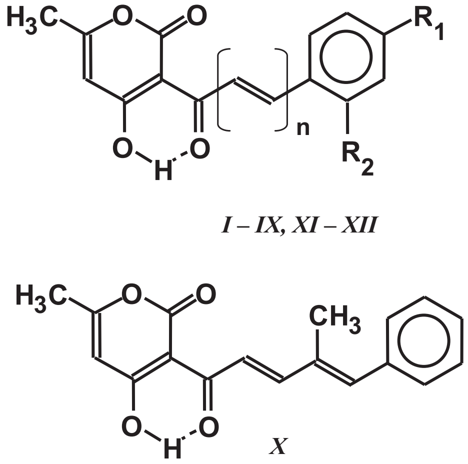


Compound	R_1	R_2	n
I	H	H	1
II	H	OCH_3	1
III	OCH_3	H	1
IV	H	$OCHF_2$	1
V	$OCHF_2$	H	1
VI	$N(CH_3)_2$	H	1
VII	$N(C_2H_5)_2$	H	1
VIII	morpholinyl	H	1
IX	H	H	2
X	H	H	2
XI	H	H	3
XII	$N(CH_3)_2$	H	2

Scheme 1. Structures of cinnamoyl pyrones investigated.

Absorption and fluorescence spectra were recorded on a Hitachi U3210 spectrophotometer and Hitachi F4010 fluorescence spectrometer, respectively. Solvents for spectral measurements were dried and purified according to methods previously described [8]. Absence of spectrally active impurities in the solvents was controlled by both spectrophotometry and spectrofluorimetry.

Mathematical treatment of the series of measured spectra, deconvolution of experimental absorption spectra into individual spectral bands and estimation of the ionization constants (pK_a) were made using the "Spectral Data Lab" software [9].

To take into account changes in injunction potential and proton activity coefficients due to going from water to the water–methanol mixture we used the equation:

$$pa_H^S = pH - \delta,$$

where pa_H^S is the proton activity in mixed solvent and δ is amendment coefficient, which was estimated as −0.06 for water–methanol (2:8, v/v) mixture [10].

Ionization constants of hydroxy groups in the excited state were estimated using Forster method [11]. Since some CP protolytic forms have no fluorescence, changes of pK_a upon excitation were calculated basing on shifts of long-wavelength absorption band maxima, and not on shifts of 0-0 transition positions [12].

The CP phosphorescence spectra and lifetimes were measured in polystyrene matrices in low-temperature cell at temperature 70 K on fluorescence spectrophotometer Cary Eclipse Varian operated in phosphorimeter mode.

The geometry optimization of CP protolytic forms, as well as the calculations of electronic density distribution in the ground state and thermodynamical parameters for protonation reaction (for ***I***) were carried out using as semi-empirical RM1 method [13] implemented in MOPAC 2009 program [14], as *ab initio* method MP2 [15] with cc-pVDZ basis set [16,17] implemented in Gaussian 93 program [18]. The influence of medium (water) polarity was modeled by the COSMO [19] and PCM [20,21] methods (for RM1 and MP2, respectively). The electronic density distribution in CP protolytic forms in the Franc–Condon excited state, and the Mulliken charges on 4-hydroxy group of α-pyrone cycle in the relaxed excited S_1 state were calculated using RM1/CI/COSMO [12] method only.

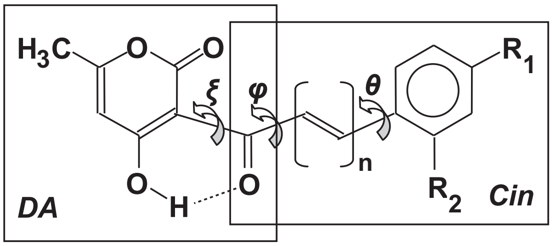
3. Results and discussion

3.1. Geometric and electronic structure of CP in the ground state. The nature of bands in absorption spectra

Cinnamoyl pyrone molecules may be presented as a superposition of two main cross-conjugated moieties – the dehydroacetic (**DA**) and cinnamoyl (**Cin**) ones (Scheme 2). The exocyclic carbonyl group belongs to both the fragments. The data listed in Table 1 show that **DA** fragment is generally plain: the torsion angle between pyrone cycle and of carbonyl group is within 2–12° range. The question concerning the flatness of **Cin** fragment is not clear. According to results obtained by RM1 method, the **Cin** fragment is not plain; its nonflatness is due to substantial torsion angles between carbonyl group, polymethine chain and phenyl ring (angles φ and θ in Scheme 2). On the contrary, *ab initio* calculations predict that most CP molecules have a planar structure.

The highest occupied molecular orbital (HOMO) in CP molecules is localized on the **Cin** fragment, while lowest unoccupied molecular orbital (LUMO) is mainly localized on the **DA** one (Fig. 1(N)). The analysis of configuration interaction matrix shows that the long-wavelength transition of CP is the one-configuration one and may be described by the HOMO–LUMO transition. Consequently, the excitation process should be accompanied by intramolecular charge transfer (ICT) between **Cin** and **DA** fragments. The charge transfer scheme in CP upon excitation is depicted in Fig. 2. The data presented in Table 1 show that the main way of the charge transfer is from phenyl cycle to exocyclic carbonyl group through polymethine chain. The value Δq_{CT} characterising ICT intensity is equal to Δq_{PP}:

$$\Delta q_{CT} = \Delta q_{PP} = \Delta q_{Cin} - \Delta q_{C=O},$$



Scheme 2. Dehydroacetic (**DA**) and cinnamoyl (**Cin**) fragments in CP molecules.