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Ultraviolet–visible study on acid–base equilibria for some 7,8-ethylenedioxy coumarins

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ABSTRACT

The UV–vis spectra of recently synthesized 7,8-ethylenedioxy coumarin, (**I**), and 7,8-ethylenedioxy-4-methyl coumarin (**II**), were studied in 5% v/v aqueous methanol. The nature of the electronic transitions and the role of methyl group of **II** in the behavior of UV–vis spectra were discussed. Acid–base equilibria of the compounds against varying pH have been examined in detail. Acid dissociation constants (pK_a) were determined at an ionic strength of 0.10 M by using the Henderson–Hasselbalch equation. The mean acidity constants for the protonated forms of the compounds were determined as $pK_a = 10.492$ ($\lambda = 259.2$ nm) for **I** and $pK_a = 10.794$ ($\lambda = 258.2$ nm) for **II**. Based on UV–Vis spectra, the preferred mechanisms for base catalyzed hydrolysis and dissociation reactions were discussed. A mechanism showing intramolecular charge transfer character of the studied molecules was also proposed.

1. Introduction

Coumarin derivatives are used in a wide range of industrial, biological and medicinal applications owing to their spectral properties. These derivatives are important for fluorescence probes [1–3] and signalling units in chemical sensors [4]. The carbonyl oxygen atom in coumarins could participate in coordinating with metal ions. Accordingly, coumarins could play a role as a binding unit in probes in analytical chemistry toward many metals and organometals, especially in spectroscopic studies for detecting metal ions [5–7]. Moreover, various coumarin derivatives have been used to modify some other compounds, e.g. phthalocyanines (Pcs) [8], cyclodextrins (CDs) [9] and azo dyes [10] with the goal of improving the efficiency in their various applications. For the medical applications, 4,5-dihydropyrazole ring was introduced into the parent 7-hydroxy-4-methyl coumarin skeleton to design novel structures with enhanced antioxidant activities [11]. In fact, a large number of medicinal plants have been chemically and pharmacologically investigated and natural chemical components possessing antihepatotoxic activities have been obtained [12]. Among them Silybin has been found to be the most potent antihepatotoxic agent containing a 1,4-dioxane ring system [13], i.e. ethylenedioxy moiety. It is therefore thought that the 1,4-dioxane ring plays an important role in causing antihepatotoxic activity and consequently some heterocyclic coumarin derivatives, possessing the 1,4-dioxane ring system have been synthesized [14–16]. Biochemical properties of some heterocyclic coumarin derivatives possessing the 1,4-dioxane ring system were also studied by Ahmed et al. [17]. It is therefore important to understand molecular properties and certain chemical phenomena, such as the binding of these molecules to environmental matrices for designing new methods of synthesis and characterization of metal complexes.

Considering the importance of the coumarin derivatives possessing 1,4-dioxane moiety, recently synthesized 7,8-ethylenedioxy coumarin,(**I**) and 7,8-ethylenedioxy-4-methyl coumarin, (**II**) may exhibit novel biological and medicinal features as many others. The structures of the compounds studied are given in Fig. 1.

As shown in Fig. 1, the compounds **I** (IUPAC name: 2H-[1,4] dioxino [2,3-h] chromen-9(3H)-one) and **II** (IUPAC name: 7-methyl-2H-[1,4] dioxino [2,3-h] chromen-9(3H)-one) are analogs of each other containing H and CH_3 groups, respectively. Compared to the coumarins, 4-methylcoumarins not only possess similar various biological activities, but are known to have less toxic properties. In particular, 4-methylcoumarins have been studied as novel antioxidants recently [18]. As shown in Fig. 1, the compounds establish one of the most popular model systems for studying acid–base properties, but up to date, no literature data is available about the chemical behavior, i.e. acid–base properties of these compounds. Such knowledge is important to understand when and where ions are distributed, released, and so on.

In previous studies, acid–base properties of some pyrimidine compounds were examined by using UV–Vis spectrometry [19,20], potentiometry [21] and cyclic voltammetry [22]. The same approach was also used in this work in order to (i) gain some insight about the species that might be present in solution at different pHs, (ii) determine their acidity constants and explain the mechanisms of protonation – deprotonation behavior, (iii) investigate the charge transfer characteristics for their differentiation and diagnosing properties, (iv) explain the effects of methyl group on such properties.

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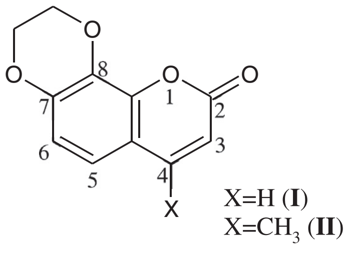

Fig. 1. Coumarins of this investigation.

Acidity constants (pK_a) of a reactant in a chemical treatment are useful physico-chemical measurements describing the extent of dissociation of functional groups with respect to pH. These parameters are also important to choose appropriate acidic or basic reagents in drug discovery and development in that knowledge of the dissociation state of a particular functional group is critical to understand the pharmacokinetic and pharmacodynamic properties of new drug substances [23].

2. Experimental

2.1. Materials

The synthesis of 7,8-ethylenedioxy coumarin, (**I**, $C_{11}H_8O_4$),and, 7,8-ethylenedioxy-4-methyl coumarin, (**II**, $C_{12}H_{10}O_4$) were described elsewhere [17]. Purity was tested by thin-layer chromatography (TLC) using benzene – methanol (8:2 v/v) solvent mixture. All chemicals were obtained from Fluka, as reagent grade materials. Triple-distilled water was used for preparation of the aqueous solutions. Preparation of water was described previously [22]. Compounds **I** and **II** are insoluble in water, therefore, the stock solutions of the compounds were prepared in an appropriate volume of absolute methanol which was used after distillation. Working solutions, 5.093×10^{-5} M for **I** and 5.499×10^{-5} M for **II**, were prepared daily in a mixture of methanol–water (5% v/v methanol). The stock solutions of the compounds were kept in dark to avoid any decomposition. IR spectra were recorded as KBr discs in the range from 4000 to 400 cm^{-1} on a Shimadzu 8300 FT-IR Spectrometer. Melting points of the compounds were measured on a Buchi 530 model instrument and correct values of the melting points were reported here. Ultraviolet–visible studies were carried out by a Shimadzu 1601 PC UV-VIS spectrophotometer with quartz cells (1.0 cm path length). The pH of the solutions prepared in a mixture of methanol–water (5% v/v methanol) was measured by a digital pH meter (Schott CG 841; ±0.001 pH unit) and a combined pH electrode that was standardized using standard aqueous buffers (pH 4.00, 7.00 and 10.00) as described in the literature [22–25]. The pH values measured were not corrected and the symbol pH (defined as $-\log [H^+]$) was used in all cases. Calibration was carried out before the experiments. An Eppendorf micro-pipette was used for the addition of solutions. A Sartorius A120 S analytical balance (sensitivity of ±0.0001 g) was used for weighing chemicals and compounds.

2.2. Measurements and procedures

Working solutions of the experiments were prepared by diluting the appropriate amount of the stock solution in methanol with aqueous Britton-Robinson (B.R.) buffer solution [26]. The final solution was 5% v/v methanol and 95% v/v water. The pH in B.R. medium was studied from pH 3.0 to 11.0 in increments of 1.0 pH unit for both compounds. For more acidic and basic solutions, 0.1 M HCl, 0.01 M HCl, 0.01 M KOH and 0.1 M KOH were used. The ionic strength of the solution was constant at 0.10 M LiCl as the supporting electrolyte. The experiments were carried out at 25 °C.

After preparation of a working solution, the pH was adjusted immediately to the desired pH by dotting with a relatively concentrated KOH or concentrated HCl on a thin glass rod. Then an appropriate volume of this solution was transferred to a 1.0-cm quartz cell and the corresponding spectrum was recorded. The absorbances (A) were determined after baseline correction. The reference beam contained a blank of the buffer containing the same amount of pure methanol as the solvent. In all experiments, UV/Vis spectra were recorded from 500.0 to 200.0 nm for each compound by using a medium scan-rate (~100 nm/min) between pH 1.0 and 13.0. The experiments were repeated at least in duplicate for each compound.

2.3. Determination of the acidity constants

The acidity constants for the protonated form of the compounds were determined from their spectral behavior in buffer solutions of varying pHs, at selected wavelengths, by using the Henderson–Hasselbalch equation as described by Albert et al. [27]. The pK_a values were calculated after baseline correction of the spectra. Additional photometric measurements in the vicinity of each pK_a value at selected wavelengths were performed using buffer solutions differing by 0.5 pH units in the mixture of methanol–water (5% v/v methanol).

3. Results and discussion

The UV/Vis spectra of both compounds in 5% v/v methanol were very similar to each other at all pH values. The spectra of each compound were characterized by two absorption maxima labeled as A, B and a weakly-separated shoulder like maximum labeled as C (hereafter shoulder C). These results agree well with the studies [28,29]. The shape of each maximum was observed approximately to be the same from pH 1.0 to 10.0. There were no significant shifts in their wavelengths and changes in their shapes within the pH range of 1.0–10.0. The absorbances for each compound were found to be almost independent of pH (data not shown). However, differences were observed in the magnitudes of three absorption maxima between pH 10.0 and 12.5. The values were strongly dependent on pH, especially at pHs between 12.0 and 12.5. As a result, significant changes were observed in the spectra of the compounds with increasing pH of the medium between pH 10.0 and 12.5.When pH was increased from 12.5 to 12.8, the spectra of the compounds were observed to change completely. Nonetheless, the spectral changes with pH show one isosbestic point at different wavelengths for each compound, indicating the presence of one acid–base equilibrium in solution. Maximum A showed the highest absorbance in the entire pH range studied. These findings indicated that the compounds were sensitive to the alkalinity of the medium. Thus, the studies were focused on the alkaline hydrolysis of the compounds by considering the fact that lactone ring opening of the coumarin nucleus may take place by hydrolysis [30,31]. The results obtained from fresh solutions of the compounds are presented below for each compound.

3.1. Effect of pH on the absorption characteristics of compound **I**

The spectra recorded for **I** in buffer solutions of different pHs in 5% v/v methanol are given in Fig. 2. The related electronic spectral data for **I** are also given in Table 1. As shown in Fig. 2, no significant change in shape of the spectra occurred for **I** from pH 9.0 to 12.0. However, changes were ocurred at pH 12.0 where maximum B decreased and the shoulder C increased simultaneously. The spectra for **I** changed completely upon increasing the pH from 12.5 to 12.8. The wavelength of maximum A was observed to shift from 319.2 nm ($\varepsilon_{max} = 12{,}780$) to 327.0 nm ($\varepsilon_{max} = 6869$), i.e. 7.8 nm red-shift when pH was raised from 9.0 to 12.5. Similarly, the wavelengths of the maximum B and the shoulder C showed red-shifts. The red-shift observed for maximum B was 15.2 nm from 259.2 nm ($\varepsilon_{max} = 6988$) to 274.4 nm ($\varepsilon_{max} = 2380$). It was 11.8 nm for the shoulder C from 225.6 nm ($\varepsilon_{max} = 3860$) to 237.4 nm ($\varepsilon_{max} = 12{,}812$). In addition, the absorbance of the maxima A and B

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