

## Synthesis of some 1,8-dioxoacridine carboxylic acid derivatives and the determination of their ionization constants in ethanol–water mixtures



Rukiye Saygılı<sup>a</sup>, Ramazan Ulus<sup>a</sup>, İbrahim Yeşildağ<sup>a</sup>, E. Kübra İnal<sup>b</sup>, Muharrem Kaya<sup>a</sup>, O. Murat Kalfa<sup>a</sup>, Bülent Zeybek<sup>a,\*</sup>

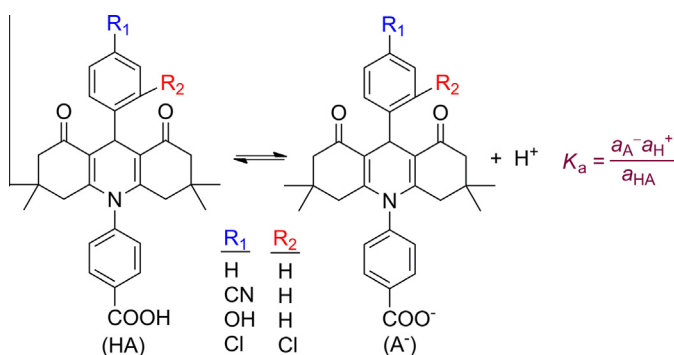
<sup>a</sup> Department of Chemistry, Faculty of Arts and Sciences, Dumlupınar University, Kütahya, Turkey

<sup>b</sup> Department of Chemistry, Faculty of Science, Ankara University, Ankara, Turkey

### HIGHLIGHTS

- Four new compounds of 1,8-dioxoacridine carboxylic acid derivatives were synthesized.
- The  $pK_a$  values of these compounds were determined by potentiometric titration method.
- This procedure was performed in ethanol–water mixtures of 50%, 60%, 70% ethanol (*v/v*).
- The effects of structure and solvent on  $pK_a$  values of these compounds were discussed.

### GRAPHICAL ABSTRACT



### ARTICLE INFO

#### Article history:

Received 29 May 2014

Received in revised form 7 November 2014

Accepted 1 December 2014

Available online 6 December 2014

#### Keywords:

1,8-Dioxoacridine carboxylic acid derivatives

Ethanol–water mixtures

Ionization constants

Potentiometric titration

Solvent effect

### ABSTRACT

Four novel compounds of 1,8-dioxoacridine carboxylic acid derivatives (4-(3,3,6,6-tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoic acid, 4-(9-(4-cyanophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoic acid, 4-(9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoic acid, 4-(9-(2,4-dichlorophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoic acid) were prepared by the reaction of the 4-substitute benzaldehyde (hydrogen, hydroxyl, cyano, and 2,4-dichloro), 4-aminobenzoic acid, and 5,5-dimethylcyclohexane-1,3-dione in the presence of *p*-dodecylbenzenesulfonic acid. They were characterized by using FT-IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, GC-MS spectroscopic techniques. The stoichiometric ionization constants of these compounds were determined in ethanol–water mixtures of 50%, 60% and 70% ethanol (*v/v*) by potentiometric titration method and the ionization constants were calculated with three different ways. The effects of solvent composition and substituent groups on ionization constants of 1,8-dioxoacridine carboxylic acids were also discussed.

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### Introduction

The acridinedione derivatives have high fluorescence efficiency and are members of a class of laser dyes [1,2]. Most of the acridin-

ediones have been used as initiators in photopolymerization of acrylates and methacrylates [2,3]. Acridines are toxic towards bacteria and especially malaria parasite because of their ability to inhibit DNA and RNA synthesis [4]. These dyes are also important because of their structural similarity to those of 1,4-dihydropyridines (DHP). The DHPs are analogous to the biologically important NADH, which are coenzymes in biological systems [1,5,6]. The DHP

\* Corresponding author. Tel.: +90 274 2652031 3222; fax: +90 274 2652056.

E-mail address: [bzeybek43@hotmail.com](mailto:bzeybek43@hotmail.com) (B. Zeybek).

derivatives are well known as the group of calcium channel blockers and have also potassium channel opener activities. They are used in the clinic as vasodilator and antihypertensive [7].

The acid-base characteristics of organic compounds are very important in various fields of chemistry and biology. The ionization constants ( $pK$ ) of organic compounds influence many characteristics such as their physical, biological and chemical properties [8]. Specially, the acidity constants ( $pK_a$ ) play a significant role to understanding the chemical reactions between the compound of interest and its pharmacological target [9]. In the literature, many of the  $pK_a$  determinations are performed in aqueous medium. However, many new compounds are poorly in aqueous solutions. Hence, in order to the determination of ionization constants of these substances should be used an organic cosolvent and the studies related with organic solvent/water mixtures has become increasingly important. Some of biological media are similar to nonaqueous solvent; hence the solvent media with water are another factor in the increased interest in such determinations [10–12].

Here we report the synthesis of novel four compounds of 1,8-dioxoacridine carboxylic acid derivatives (4-(3,3,6,6-tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoic acid (**acid 1**), 4-(9-(4-cyanophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoic acid (**acid 2**), 4-(9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoic acid (**acid 3**), 4-(9-(2,4-dichlorophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoic acid (**acid 4**)). For the characterization of these compounds were used FT-IR,  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , GC-MS spectroscopic techniques. The stoichiometric ionization constants of the four acidic compounds were determined in ethanol–water mixtures of 50%, 60% and 70% ethanol ( $v/v$ ) by potentiometric titration method in order to effective use of these compounds, which have important pharmaceutical potential. Furthermore, the changes in the ionization constants with the structures of the compounds and composition of the solvent were examined.

## Experimental

### Chemicals and apparatus

5,5-Dimethylcyclohexane-1,3-dione, 4-aminobenzoic acid, benzaldehyde; 4-cyano-benzaldehyde, 4-hydroxybenzaldehyde, 2,4-dichlorobenzaldehyde, *p*-dodecylbenzenesulfonic acid reagents were purchased from Sigma–Aldrich. All chemicals and solvents used for the synthesis were spectroscopic reagent grade.

For the potentiometric studies, stock solutions of 1,8-dioxoacridine carboxylic acids were prepared in ethanol (Sigma–Aldrich, GC grade). These compounds are slightly soluble in water; hence, the determinations of ionization constants are performed in water–ethanol mixtures. All other chemicals were analytical grade. Stock solutions of standard base and acid were prepared using sodium hydroxide (Merck) and hydrochloric acid (Sigma–Aldrich), respectively. The solutions of sodium hydroxide containing  $0.10 \text{ mol L}^{-1}$  NaCl (Merck) were prepared in 50, 60 and 70% aqueous ethanol solutions ( $v/v$ ) and were standardized potentiometrically against potassium hydrogen phthalate (Merck). The solutions of hydrochloric acid were prepared in 50%, 60% and 70% aqueous ethanol solutions which were standardized by titration against standard sodium hydroxide solutions by the use of Gran's plot techniques, allowing the determination of dissolved carbonate impurities [13]. Pure sodium chloride was employed to maintain a constant ionic strength ( $I = 0.1$ ). For this purpose,  $1.0 \text{ mol L}^{-1}$  NaCl stock solution was prepared and then certain volumes of this stock

solution were added during the preparation of the sodium hydroxide, hydrochloric acid and the 1,8-dioxoacridine carboxylic acid solutions and also the titration cell where the final NaCl concentration was to be  $0.1 \text{ mol L}^{-1}$ . So, the ionic strength of the medium was constant at the value of 0.1.

Melting points were measured on a Bibby Stuart Scientific apparatus. FT-IR spectra were recorded from Bruker Optics, Andrtex 70 FT-IR spectrometer with an ATR diamond crystal.  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra were obtained with a Bruker DPX-300 FT-NMR instrument in  $\text{CDCl}_3$  or  $\text{DMSO-}d_6$  as a solvent, at 300 MHz. Chemical shifts are expressed in  $\delta$  units (ppm). The mass analyses were performed by Shimadzu GCMS-QP2010 Plus Gas Chromatography/Mass Spectrometer.

### The general procedure for preparation of 1,8-dioxoacridine carboxylic acid derivatives

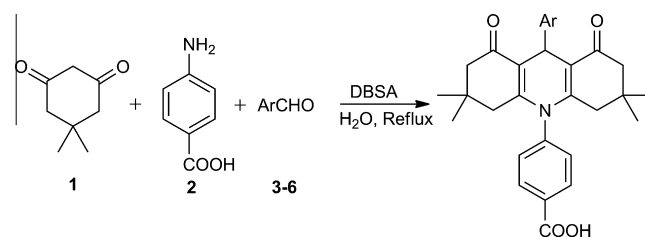
A mixture of 5,5-dimethylcyclohexane-1,3-dione (**1**; 0.280 g, 2 mmol), 4-aminobenzoic acid (**2**; 0.157 g, 1.0 mmol), benzaldehyde group (**3–6**; benzaldehyde; 4-cyanobenzaldehyde; 4-hydroxybenzaldehyde; 2,4-dichlorobenzaldehyde, 1.0 mmol) and *p*-dodecylbenzenesulfonic acid (DBSA, 0.420 g) in water (40 mL) was stirred at refluxing for 5–6 h. The reactions process was observed by TLC. When the reaction was ended, the mixture was cooled to room temperature. The cool mixture was filtered and washed with 500 mL water. The solid product was recrystallized with solvent mixture of ethanol (90%). 1,8-Dioxoacridine carboxylic acid derivatives were obtained as pure (70–90%). The general procedure for synthesis of 1,8-dioxoacridine carboxylic acid derivatives was given in the Scheme 1.

### 4-(3,3,6,6-Tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoic acid (Acid 1)

As yellow crystals, (0.364 g, 78%), mp  $320 \text{ }^\circ\text{C}$  (dec.) (ethanol–water).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm): 0.70 (s, 6H,  $2\text{CH}_3$ ), 0.85 (s, 6H,  $2\text{CH}_3$ ), 1.76 (d, 2H,  $J = 17.38 \text{ Hz}$   $-\text{CH}_2$ ), 2.01 (d, 2H,  $J = 19.46 \text{ Hz}$   $-\text{CH}_2$ ), 2.18 (d, 2H,  $J = 3.56 \text{ Hz}$   $-\text{CH}_2$ ), 2.23 (d, 2H,  $J = 5.04 \text{ Hz}$   $-\text{CH}_2$ ), 5.05 (s, 1H,  $-\text{CH}$ ), 7.10 (t, 1H,  $J = 14.31 \text{ Hz}$  Ar–H), 7.25 (t, 2H,  $J = 15.09 \text{ Hz}$  Ar–H), 7.32 (d, 2H,  $J = 7.01 \text{ Hz}$  Ar–H), 7.55 (d, 2H,  $J = 8.35 \text{ Hz}$  Ar–H), 8.15 (d, 2H,  $J = 8.56 \text{ Hz}$  Ar–H), 13.30 (br, 1H,  $-\text{COOH}$ );  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm): 26.49, 29.68, 32.40, 32.48, 41.34, 50.04, 56.49, 113.56, 126.28, 128.00, 130.63, 131.45, 132.05, 142.71, 146.58, 150.33, 166.97, 195.55. IR ( $\text{cm}^{-1}$ ): 3400 between 2400 br (Ar–COOH), 3122 and 3081 w (Ar–H), 2952 w (C–H), 1726 and 1635 s (C=O), 1598 and 1558 m (C=C), 1362 s (C–N), 1211 s (C–O); MS(Cl)  $m/z$  469 (30%).

### 4-(9-(4-Cyanophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoic acid (Acid 2)

As yellow crystals, (0.385 g, 79%), mp  $330 \text{ }^\circ\text{C}$  (ethanol–water).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm): 0.72 (s, 6H,  $2\text{CH}_3$ ), 0.89 (s, 6H,



Scheme 1. The structures of 1,8-dioxoacridine carboxylic acid derivatives.

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