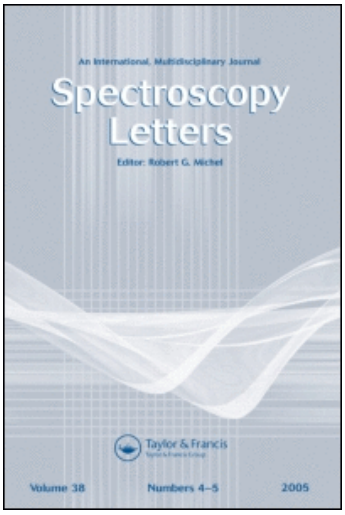

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Spectroscopic Analysis of the Ionization Behavior of Anthralin

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SPECTROSCOPIC ANALYSIS OF THE IONIZATION BEHAVIOR OF ANTHRALIN

Keywords: Anthralin, Ionic Equilibria, Spectrophotometry, Intramolecular Hydrogen Bonding, Temperature Coefficient, pK_a

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ABSTRACT

The ionic equilibria of anthralin were examined at 25°C in aqueous solutions varying in pH from 5.10 to 11.74. Despite the presence of three phenol groups, only one pK_a was observed under these experimental conditions and even at pH = 11.74 there was no spectroscopic evidence for the presumed second pK_a. Possible causes for this result are discussed. The experimentally observed pK_a was 9.06 which yielded a thermodynamic pK_a estimate of 9.38. These results agreed well with one of two conflicting reports in the literature.

INTRODUCTION

Anthralin (1,8,9-anthracenetriol) has been used in the treatment of psoriasis for over sixty years.[1,2] Recently, there has been increased interest in the proper formulation of this compound in

order to maximize the therapeutic effect while minimizing unpleasant side effects.[2] Optimization of topical drug delivery systems requires knowledge of, amongst other things, the drug's chemical stability, release characteristics from the formulation matrix, and ability to partition into the stratum corneum (also a function of the formulation). Accurate characterization of these phenomena require that the ionic equilibria of the species present be well known. Two available reports of the pK_a of anthralin differ appreciably.[3,4] In this study a spectrophotometric approach was employed that allowed data to be obtained rapidly, thus eliminating ambiguity due to decomposition of this labile drug, as well as obviating the need for nonaqueous cosolvents.

MATERIALS AND METHODS

Anthralin was obtained from Aldrich and was kept refrigerated (5°C) in a desiccator. Tris(hydroxymethyl)aminomethane was of primary standard grade and was obtained from Sigma Chemical Company. Anhydrous sodium acetate (certified A.C.S.), glycine (reagent grade), certified sodium hydroxide (1N) solution and hydrochloric acid (1N) solution, as well as potassium chloride (certified A.C.S.) were purchased from Fisher Scientific Company. Ethanol (95%, U.S.P. grade) was from Pharmco Products Inc. All buffer solutions were prepared in double-distilled water (all glass distillation apparatus). The absorbance spectra of anthralin were obtained with an HP8450A photodiode array, double-beam, parallel detection UV-VIS spectrophotometer equipped with a temperature control station and a

thermo-electric cell holder. Aliquots of anthralin stock solution in 95% ethanol were diluted appropriately into several buffer solutions containing acetic acid-sodium acetate, tris-hydrochloric acid or glycine-sodium hydroxide buffer systems. The final concentration of ethanol in any solution was one percent. The pH values of the aqueous solutions were measured with a Model 611 digital pH meter and a Ag/AgCl glass electrode (Orion Research) in a 50 ml water-jacketed beaker maintained at 25.0 ± 0.1°C. UV cells (Spectrocell) with 10 mm light paths and 3.5 ml volumes were employed. Ambient light was reduced and the absorbance spectra were recorded from 220-800 nm. Ten (10) second integration times were used in this study providing an average of twenty individual spectra per measurement. The balance measurements were made using the appropriate buffer solution at each experimental pH condition.

RESULTS AND DISCUSSION

Spectrophotometry is advantageous for this study because anthralin is too insoluble for a completely aqueous titration and spectrophotometric methods exhibit high sensitivities for substances with large molar absorptivities.[5] At a pH of 10.00, where both ionized (~90%) and unionized anthralin species were present, the apparent, or overall, absorptivity was 67000 1 $mole^{-1}$ cm^{-1} at 258 nm. Further, the technique depends upon the direct determination of the ratios of the neutral and/or ionic species present in a series of buffer solutions of varying pH. Beer's law must be obeyed for both species and this was demonstrated by the data in Figure 1. The

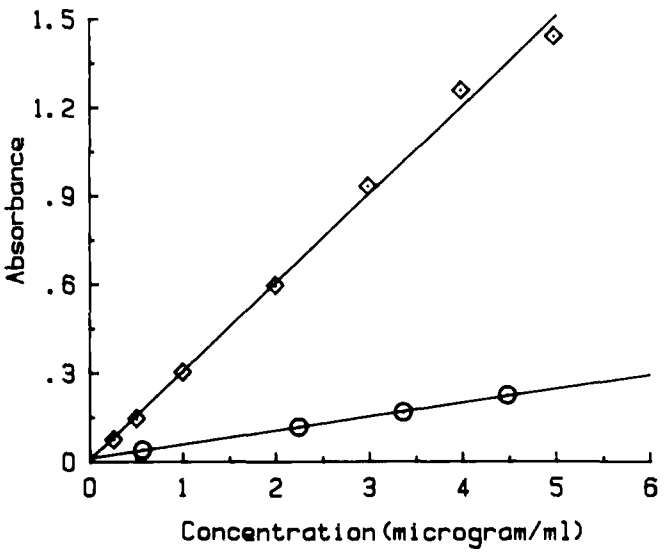

FIG. 1. Beer's law plots for anthralin at 258 nm. The solid lines were obtained by linear least squares regression analysis: o, pH 7.54 (Correlation Coefficient = 0.9996); □, pH 10.00 (Correlation Coefficient = 0.9977).

absorbance spectra as a function of pH are shown in Figure 2. The analytical wavelength chosen was 258 nm since a maximum change in absorptivity with pH occurred at this wavelength. The absorbance at pH 5.10 served as the absorbance of the pure molecular species and that at pH 11.74 as the absorbance of the completely ionized species. Since ionic strength (μ) may change significantly with pH as a result of change in the degree of ionization of the buffer and/or the test compound, the ionic strength of the solutions was maintained at 0.5 M by the addition of appropriate amounts of

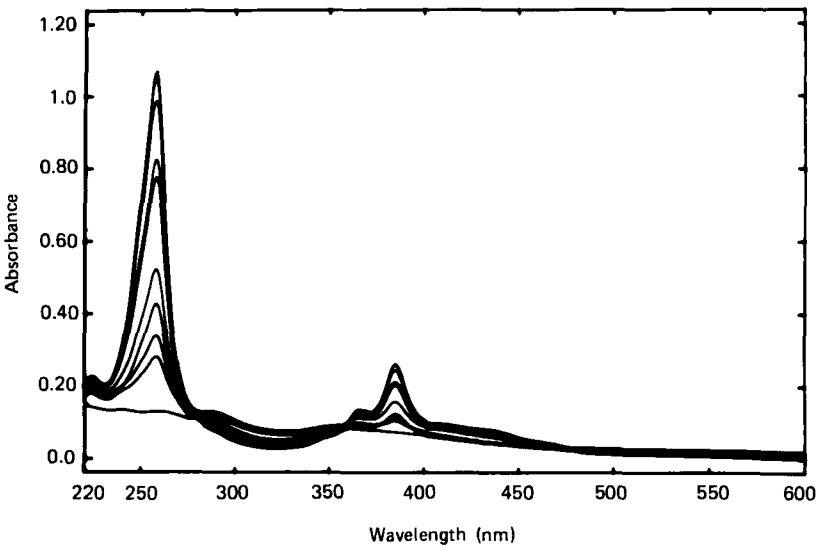

FIG. 2. Absorption spectra of anthralin as a function of pH

potassium chloride. Failure of spectral curves to intersect at a well-defined isosbestic point generally indicates medium effects on the spectra, compound decomposition, or the presence of impurities. The appearance of a well-defined isosbestic point is necessary for meaningful measurements[5] and two such isosbestic points were observed in this study (Fig. 2): one at 279 nm and the other at 360 nm.

The pK_a value for anthralin was derived from the appropriate form of the Henderson-Hasselbach equation:

$$pK_a = pH + \log \left[\frac{A_I - A}{A - A_m}\right] \qquad \text{Eqn. 1}$$

where A_I is the absorbance of the fully ionized species, A_m is the absorbance of the pure molecular species, and A is the observed

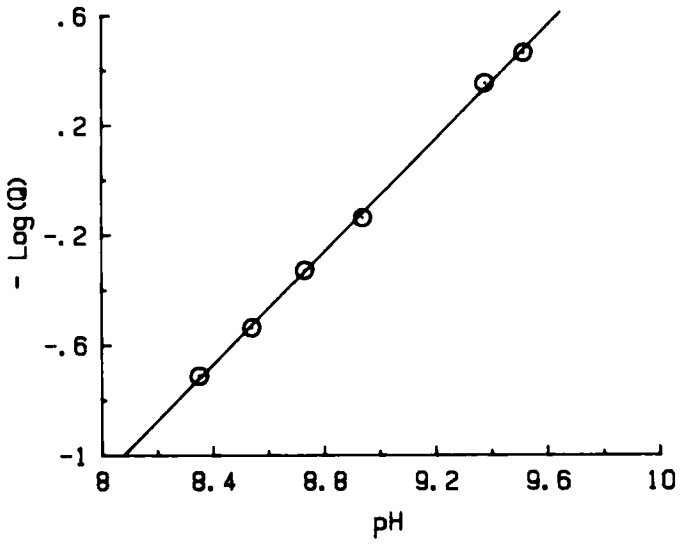

FIG. 3. Graphical determination of the pK_a of anthralin according to eqn. 2

sample absorbance at any pH. Absorbance can be used in place of absorptivity when total drug concentration has been shown to be constant from sample to sample by a well-defined isosbestic point. The above equation can be rearranged to:

$$-\log Q = pH - pK_a \qquad \text{Eqn. 2}$$

where

$$Q = \left[\frac{A_I - A}{A - A_m}\right]$$

The plot of -log Q vs. pH is shown in Figure 3 and pK_a is equal to pH when the quantity Q becomes unity. In addition, point-by-point calculations were performed using Equation 1. The resultant pK_a

values were converted to K_a values, averaged, and the mean K_a was transformed back to a pK_a. Both calculational methods yielded a pK_a value of 9.06. The same pK_a value should be obtained irrespective of wavelength and the value of 9.07 calculated from the absorbances at 385 nm thus provided useful verification. As expected, there is a substantial difference between the value reported in this study and the value of 13.06 reported by Kido et al.[3] in a mixed solvent system. Melo et al.[4] reported an aqueous pK_a value of 9.4 at 20°C but μ was not reported. If it is assumed that 9.4 is the thermodynamic pK_a, then it can be readily converted to the value appropriate for a temperature of 25°C and an ionic strength of 0.5 M. Application of an appropriate temperature coefficient correction ($d(pK_a)/dT = -0.013$ for phenols[6]) and an appropriate activity coefficient correction yielded a pK_a value of 9.01. This is in good agreement with the value reported in this paper. In similar fashion, the experimentally obtained pK_a of 9.06 results in a thermodynamic pK_a estimate of 9.38 at 25°C.

Although anthralin (I) has three dissociable protons as a result of its three phenol groups, no evidence of either the second or the third ionization reactions were observed in this study. This can be explained by considering the equilibrium I $\rightleftarrows$ II (Fig. 4). It can be seen that the hydrogen atoms in form II can be more strongly intramolecularly hydrogen bonded than is possible in form I. This renders the molecule much less susceptible to further deprotonation and the concentration of the abstracting base must be greatly increased to achieve form III. This argument follows that

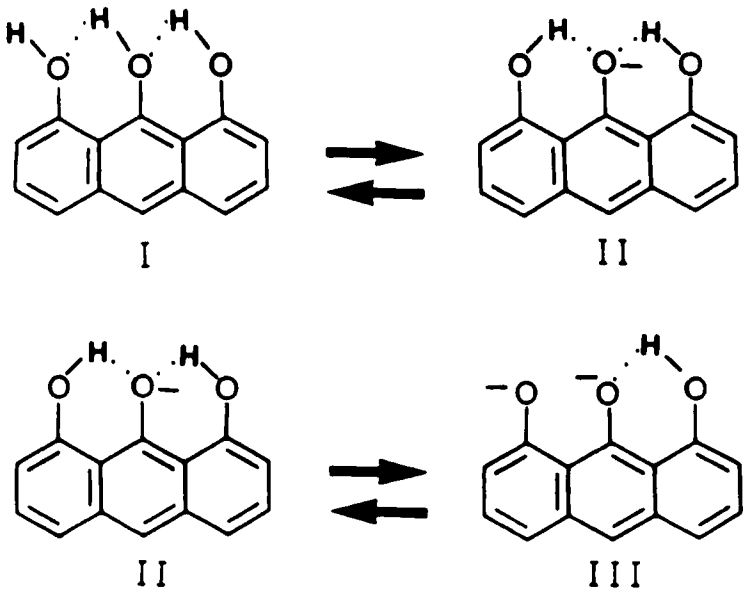

FIG. 4. Ionization equilibria of anthralin.

proposed for salicylic acid wherein the extraordinarily high second pK_a (13.6, 20°C) is ascribed to strong intramolecular hydrogen bonding in the singly-charged anion.[7] An additional consideration is the coulombic repulsion arising from the proximity of the two negative charges in form III which also renders the II $\rightleftarrows$ III equilibrium less favorable. Both of these factors are presumably represented in the reported[8] pK_a values (6.71, >13, both at 20°C) of 1,8-naphthalene diol; a compound with obvious structural similarities to anthralin. While other supporting examples can be found,[9] the important conclusion is that for all physicochemical studies of anthralin that have physiological, pharmacological, or pharmaceuti-

cal importance, only one pK_a needs to be considered. This pK_a is now accurately known.

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