Medium Effect on the Deprotonation Constants of 2-(p-Dimethylaminostyryl)pyridine & 2-(p-Dimethylaminostyryl)quinoline Ethiodides

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The visible absorption spectra of 2-(p-dimethylaminostyryl)pyridine- and quinoline-ethiodides have been recorded in water-organic solvent mixtures at different pH values. The solvents used include methanol, ethanol, acetone, dimethylformamide and dimethylsulphoxide. The deprotonation constants values in different media have been determined and are discussed in relation to the nature and amount of the organic solvent. Generally the pK values decrease with increasing proportion of the organic solvent and as the polarizability of the organic solvent molecule increases. It is concluded that the stabilization of the base by dispersion forces exceeds that from hydrogen bonding. The free energy of solvation of the base and proton by dispersion forces and ion-solvent interactions have been calculated. The effect of solvent polarity on the band position is discussed.

A PERUSAL of literature reveals that the ionization constants data of styryl-quinoline or pyridine derivatives are scanty. It is known that these derivatives can serve as useful intermediates in the preparation of compounds known to possess valuable pharmacological properties. The anticarcinogenic activity of styryls of diverse structure was previously indicated by a number of authors. Styrylpyridine or quinoline derivatives have been recognized as photosensitizers and desensitizers.

The effectiveness of the styryl dyes as photosensitizers increases when they are present in the non-protonated or ionic form which probably has greater planarity. To this end the present work deals with the effect of pH on the deprotonation of 2-(p-dimethylaminostyryl)pyridine-(I) or quinoline(II)-ethiodides in the presence of the organic solvents methanol, ethanol, acetone, dimethylformamide and dimethylsulphoxide. The pK values have been determined and will be discussed with reference to the nature of the solvent.

Materials and Methods

The compounds used in the present investigation were prepared by the condensation of α-picoline or quinaldine ethiodide with p-dimethylaminobenzaldehyde in the presence of piperidine under experimental conditions given by Phillips. The products obtained were crystallized from ethanol.

Solutions (10−3M) of the compounds were prepared by dissolving the appropriate amount of the solid in the organic solvent. More dilute solutions were prepared by accurate dilution. The organic solvents used were of spectroscopic grade. The modified universal buffer series was prepared as reported by Britton and Robinson. The pH of the solutions were checked at 25°C using a Unicam model 290-MK2 pH-meter, reading to ±0.005 pH units.

The absorption spectra were recorded on a Unicam SP 8000 spectrophotometer using 1 cm matched quartz cells. All measurements were carried out at 25°C.

The measured pH values of the aqueous buffer solutions containing varying proportions of the organic solvent used in this investigation have been corrected in accordance with the method described by Douheret. Thus if the pH-meter is standardized using aqueous buffers, the meter reading \( \text{pH}(R) \) obtained in a partially aqueous medium differs by an amount \( \delta \), from the corrected reading \( \text{pH}* \) which is referred to the standard state in the partially aqueous solvent,

\[
\text{pH}^* = \text{pH}(R) - \delta
\]

The values of \( \delta \) for the aqueous buffer solutions containing varying proportions of each of the organic solvents under investigation were determined by Douheret.

Results and Discussion

The spectra of solutions of I and II of constant concentration were recorded as a function of pH in the presence of various amounts of different organic solvents. Solutions of low pH display a band with \( \lambda_{\text{max}} \) at shorter wavelengths which is nearly solvent independent and correspond to the absorbance of the protonated form. With increasing pH, the absorbance of the band decreases, while another band develops at longer wavelength the position of which is dependent upon the solvent composition.

The high blue shift (108 nm) of the band in solutions of low pH's relative to ones of higher pH's is presumably due to the fact that the transition.
corresponding to this band is highly influenced by
intramolecular charge transfer originating from the
N(CH₃)₂ group to the heteronitrogen atom. In the
former solutions the N(CH₃)₂ group is protonated
and consequently its donor character decreases.
In each solvent system, the spectra show clear
isosbestic points in accordance with the equilibrium:

The variation of absorbance with pH (Fig. 1) is
utilized for the determination of the deprotonation
constants of the compounds. For this purpose
three different spectrophotometric methods were
applied: (i) half-height method; (ii) the limiting
absorbance method; and (iii) The Collette method
modified for acid-base equilibria. The results
obtained are given in Table 1.
The deprotonation constants \( K_1 \) of I and II
in pure aqueous medium may be related to that
\( K_2 \) in partially aqueous medium by means of the
activity coefficients of the various species involved
in the equilibrium in partially aqueous medium
to a standard state in the pure aqueous medium
by Eq. (1):

\[
K_1 = K_2 \gamma_{H^+} \gamma_{A^+} / \gamma_{H^+A^+}
\]

Fig. 1 - Absorbance-pH curves at 430 nm for compound
(l) in the presence of different amounts (w/w) of methanol
in aquo-organic solvent medium [Methanol (% w/w): (a) 0.0,
(b) 7.92, (c) 15.84, (d) 23.76 and (e) 31.68]

<table>
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<th>% (w/w) of organic solvent</th>
<th>Dielectric constant of the medium at 25°C</th>
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<th>Compound (II)</th>
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Table 1 — Mean pH Values for 2-(p-Dimethylaminostyryl)pyridine (I, 4.0 x 10⁻³ M) and
Quinoline (II, 1.15 x 10⁻⁵ M) Ethiodides and the \( \lambda_{max} \) Values of the Protonated and Non-Protonated Forms in
Water-Organic Solvent Mixtures
From the results in Table 1, it is evident that the deprotonation constants decrease with increasing percentage of the organic solvent (methanol, ethanol, acetone, DMF, DMSO) in the medium. This behaviour indicates that effects other than the dielectric constant (electrostatic effect) play an important role. This suggestion gets support from the fact that the electrostatic effect on the activity of the proton, free base (A+) and on that of the acid (H+A+) will cancel to a large extent and thus will have only a relatively small influence on the deprotonation constants of these compounds.

This behaviour can be supported by calculating the change in the deprotonation constant produced by electrostatic effect \( \Delta pK_{el} \) for both the compounds I and II in the presence of the high percentage of each organic solvent used (cf. Table 2). These values were calculated making use of Born equation\(^{14}\), known to be more valid when large radii are considered\(^{21}\), and following the principles described by Tremblion\(^{33}\). Thus for the above equilibrium, Eq. (2) can be applied for calculation of \( \Delta pK_{el} \).

\[
\Delta pK_{el} = -\frac{N e^2}{4 \pi \varepsilon R T} \left( \frac{1}{r_{H+A^+}} - \frac{1}{r_{A^+}} - \frac{1}{r_{H^+O}} \right) \left( \frac{1}{\Sigma_{\text{solvent}}} - \frac{1}{\Sigma_{\text{water}}} \right)
\]

(2)

where \( N = \) Avogadro's number, \( e = \) electron charge, \( r = \) radius of ion expressed in Å, \( \Sigma = \) dielectric constant.

In order to determine the radius of the doubly charged cation \( (r_{H^+A^+}) \), its density is considered to be approximately equal to the one of the corresponding nonquaternized derivative. The densities of the nonquaternized derivatives of I and II were determined by the technique originally designed by Clark and White\(^{10}\). The values obtained are 1.455 and 1.2975 g/cm\(^3\) respectively. The calculated radii of the nonquaternized derivatives of I and II are 4.40 and 4.52 Å respectively. It is worthy to mention that the radii of the protonated and non-protonated cations (H+A+ and A+) are of the same order of magnitude and \( r_{H^30} = r_{H^2O} = 1.93 \) Å.

It is known that the properties of solvents such as dielectric constant, acidic strength and basic strength play a major but not exclusive role. Other factors such as stabilization of the different species existing in equilibrium through hydrogen bonding together with ion-solvent interaction and dispersion forces play an important role in the ionization of weak acids. Accordingly, the observed decrease in \( pK \) of the compounds under investigation can be mainly ascribed to the following effects:

(i) In partially aqueous media, stabilization of the base by dispersion forces exceeds that from hydrogen bonding. This dispersion interaction is established between the delocalized oscillator dipole of the conjugate base and the localized oscillator dipole of the solvent. The base form of compound I can be represented by structure (III).

\[
\text{(III)}
\]

It is expected that the effective density of dispersion centres of the solvents under investigation will increase in the sequence: water < methanol < ethanol < acetone < DMF < DMSO. This

| Table 2 — Values of \( \Delta pK_{el} \), \( \Delta pK_{nonel} \), \( \Delta G_{el} \), and \( \Delta G_{nonel} \) Obtained for Compounds I and II (\( \Delta G's \) at 25°) |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| +\( \Delta pK_{el} \) | -\( \Delta pK \) | +\( \Delta G_{el} \) kcal/mol | -\( \Delta G_{el} \) kcal/mol | +\( \Delta G_{nonel} \) kcal/mol | -\( \Delta G_{nonel} \) kcal/mol |
| I | II | I | II | I | II | I | II | I | II |
| 0.04 | 0.04 | 0.75 | 0.82 | 0.055 | 0.055 | 1.03 | 1.12 | 1.09 | 1.18 |
| 0.034 | 0.034 | 0.95 | 0.92 | 0.047 | 0.047 | 1.30 | 1.26 | 1.350 | 1.31 |
| 0.03 | 0.03 | 1.07 | 0.96 | 0.041 | 0.041 | 1.47 | 1.32 | 1.51 | 1.36 |
| 0.01 | 0.01 | 1.03 | 1.02 | 0.014 | 0.014 | 1.40 | 1.41 | 1.41 | 1.42 |
| 0.006 | 0.006 | 0.98 | 0.95 | 0.008 | 0.008 | 1.34 | 1.30 | 1.35 | 1.31 |

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increase was previously indicated by Alfenaar and Deligny. Accordingly, one must expect an apparent increase in the stability of the conjugate base by dispersion interaction forces as the amount of the organic solvent in the medium increases. The effect of dispersion force on acid-base equilibrium was previously indicated by several authors.

(ii) The greater stabilization of the proton is achieved by its interaction with organic solvent and water molecules in the mixture than that with water molecules alone (ion-solvent interaction). This is presumably due to the high electron density on the oxygen atoms of the solvent molecules.

The above two mentioned effects will result in decreasing the activity coefficients of both the base and the proton in solvent-water mixtures relative to that in pure water. This must lead to an increase in the deprotonation constant (low $pK$ value) of the compounds under investigation as the percentage of the solvent in the aqueous medium increase as indicated from Eq. (1).

On comparing the values of $pK$ obtained for different solvent-water media having the same composition (Table 1), one can easily find out that the deprotonation constant is dependent on the nature of the non-aqueous component in these media. However, the decrease of the $pK$ values with the nature of the organic solvent used in this investigation were found to follow the order: DMSO < DMF < acetone < ethanol < methanol. This is expected as a result of the decrease in the solvent polarizability on going from DMSO to methanol within the above sequence.

This behaviour strongly supports the fact that the high stabilization of the non-protonated form by dispersion forces and of the proton by its interaction with solvent are the two important factors responsible for the decrease in $pK$ of the compounds under investigation as the percentage of the solvent in the medium is increased.

The free energy of solvation of the base and the proton by dispersion forces and ion-solvent interaction respectively, which is equal to the free energy of transfer due to nonelectrostatic interaction ($\Delta G_{nlec}$) in the presence of the higher percentage of each of the organic solvent used was calculated and the values obtained are recorded in Table 2. It is evident that the free energy of solvation becomes more negative as the solvent polarizability increases, indicating a high stabilization of both the base and proton on going from methanol to DMSO as explained above.

An examination of the results given in Table 1 shows that the band responsible for the absorption of the base exhibits an observed red shift in its $\lambda_{max}$ as the amount of the solvent in the medium increases. This red shift is presumably due to the fact that increase in the concentration of the organic in the medium, will increase the extent of dispersion forces between the base and the solvent molecules. This in turn will increase the proportion of the polarized structure of the base in solution and consequently an easy intramolecular charge transfer is expected to occur.

References