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Spectral and Electrochemical Studies of Phenazopyridine

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Abstract: The spectral and voltammetric behavior of phenazopyridine (**1**) in aqueous buffers of varied pH is presented. Spectrophotometry, cyclic voltammetry, differential pulse polarography and coulometry were utilized to study its proton and electron transfer characteristics. Relevant thermodynamic and electrochemical data such as pK_a , charge transfer co-efficient (α_{na}), forward rate constant ($K_{f,h}^0$), etc., have been evaluated. An excellent electroanalytical method of assaying of **1** has been developed in differential pulse polarography at pH = 8. Molecular modeling on various acid-base conjugates of **1** and their several conformers has been carried out to arrive at the thermodynamic and conformational issues to correlate the spectral and electrochemical observations.

Keywords: Phenazopyridine, Acid-base equilibria, Cyclic voltammetry, Molecular modeling, Isosbestic points, Conformers

Introduction

Aromatic azo compounds constitute a very important class of organic compounds because of their optical, electrochemical and medicinal relevance¹⁻³. Their optical properties are exploited in dye industry and as indicators of acid-base titrations. The facile and intense voltammetric response due to the reduction of -N=N- into -NH-NH- and -NH₂, has been providing a great deal of information about their optical, structural, electrochemical and thermodynamic properties⁴⁻¹².

Phenazopyridine (**1**), which is 2,6-diamino-3-(phenylazo)pyridine, is a urinary tract analgesic, commercially available as Pyridium® tablets. We present here the first electrochemical investigations of this drug in aqueous buffers of varied pH besides some spectral and molecular modeling studies.

Experimental

Several phenazopyridine tablets were crushed and leached into warm water and then the drug was regenerated by slowly adding NaHCO_3 solution. It was recrystallized from methanol. A millimolar stock solution of **1** was prepared in methanol. Before the spectral or electrochemical run, 1 mL of the stock solution was placed in a 25 mL standard flask and was made up by the Britton-Robinson¹³ buffer of the desired pH (ionic strength = 0.02 M). The corresponding blank solution was similarly made by just making up 1 mL of methanol. An ATI Orion Model 902 Ion Meter was used for the pH-metry whereas an AnalyticJena Specord 205 Ratio Recording Spectrophotometer for UV-Vis spectra and a Metrohm 663 VA Stand for voltammetric (on mostly an SMDE) and a BAS CV-27 Voltammograph for coulometric studies. Molecular modeling was carried out on a ChemOffice Ultra Pro 10.0 platform.

Results and Discussion

Spectral studies and acid-base equilibria

The electronic spectra of **1** at three different pH are shown in Figure 1. A slight hypsochromic shift is observed, with the presence of isosbestic points at 325, 395 and 470 nm, as pH increases. The aqueous spectrum of **1** at high pH (>6) is near-similar to whereas that at low pH (<5) is slightly different from the isotonic methanolic solution spectrum of **1**. This fact suggests that **1** exhibits a protonation-deprotonation equilibrium in aqueous buffers. A plausible tautomeric (vertical arrows) and acid-base (horizontal arrows) speciation equilibrium for **1**, is shown in Scheme 1.

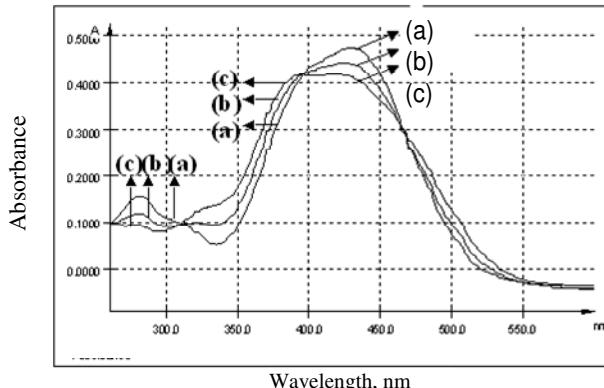
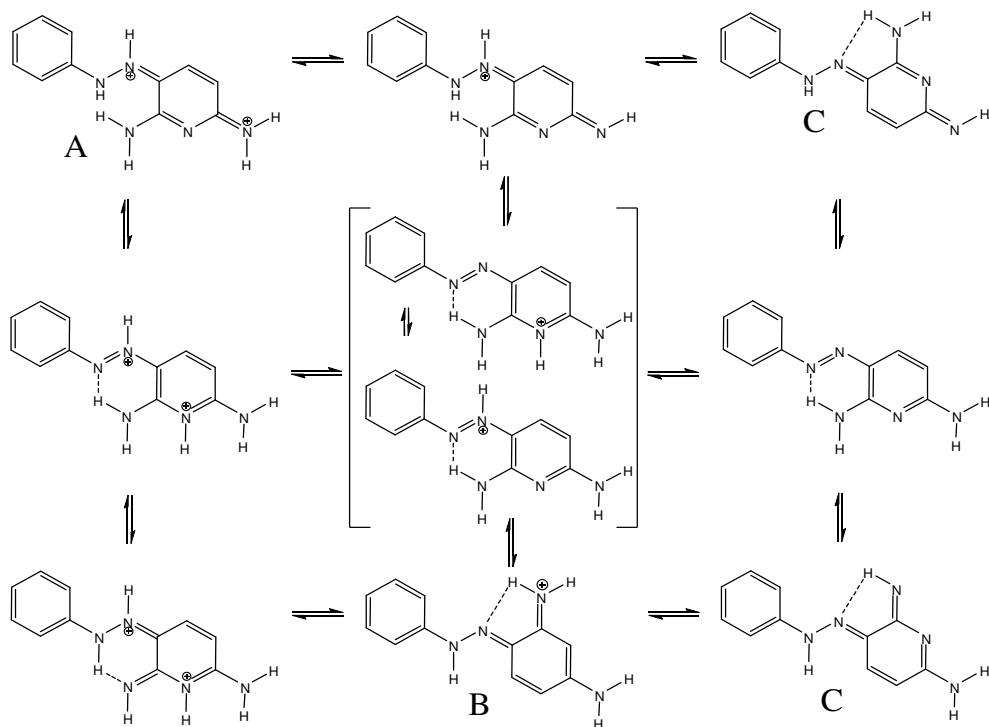


Figure 1. UV-Vis spectra of **1** at pH (a) 2.56, (b) 4.02 and (c) 5.93.

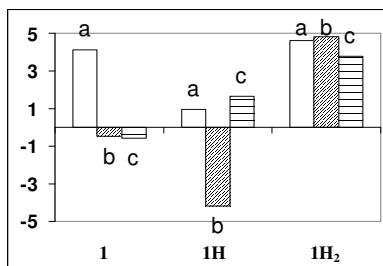
The electronic spectral band that shifts from 430 nm to 390 nm with increased pH, is expected to be due to $n \rightarrow \pi^*$ transition of the azopyridine moiety. There has been a debate on the site of protonation in azobenzenes. Earlier proposals assume that the proton binds symmetrically to both the nitrogen atoms^{14,15}. Molecular modeling was performed on various tautomers and conformers possible for $\mathbf{1H}^{2+}$, $\mathbf{1H}^+$ and **1**. Finally, for each of $\mathbf{1H}^{2+}$, $\mathbf{1H}^+$ and **1** a set of three most stable isomeric forms (on the basis of their least heats of formation arrived at by energy minimization in MM2 force field) has been selected and the same only are presented in Scheme 1. All other tautomers and conformers are discarded for brevity. Each of this most stable sets consists of a π -delocalized benzenoid form (form **a**), *ortho*-quinonoid form (form **b**) and *para*-quinonoid form (form **c**) at the azopyridine moiety as shown in Scheme 1.

**Scheme 1.**

The heats of formation for various of these forms of $\mathbf{1H}^{2+}$, $\mathbf{1H}^+$ and $\mathbf{1}$ are presented in Table 1. The same are also graphically shown in Figure 2. From this table and figure it is indicated that conjugate, $\mathbf{1H}_2^{2+}$ exists predominantly in form **c**. This is not unexpected because it is only in this form that $\mathbf{1H}^{2+}$ keeps its two protonated positive charge centers at the farthest positions to avoid electrostatic repulsion. However, $\mathbf{1H}^+$ is most stable in form **b** whereas the parent molecule, $\mathbf{1}$, prefers any of **b** or **c**. The most stable forms for $\mathbf{1H}^{2+}$, $\mathbf{1H}^+$ and $\mathbf{1}$ are indicated by labels **A**, **B** and **C** respectively in Scheme 1. Since transition from species **A** to **B** is accompanied by a greater electronic change than that from **B** to **C**, considerable spectral change is expected when pH is altered from a very low pH to a moderate pH. By plotting the slope of absorbance with pH at 430 nm against the pH, the value of pK_a and thereby the ΔG^0 of the deprotonation process has been evaluated. They are found to be 4.35 and 23.82 kJ mol⁻¹ respectively. The size and sign of these values do not go well for the process of $\mathbf{1H}^{2+} \rightarrow \mathbf{1H}^+$ but do for $\mathbf{1H}^+ \rightarrow \mathbf{1}$ because a value of pK_a more than 1 means a positive Gibbs free energy change. This is also supported from the facts that deprotonation of $\mathbf{1H}^+$ from species **B** to yield $\mathbf{1}$ in species **C** does not accompany with any considerable electronic density variation at the azopyridine site and that the spectral change seen in Figure 1 is very small. Deprotonation of the pyridine nitrogen would hardly alter the electronic characteristics of the extended conjugation because the lone pair of electrons of the pyridine ring is orthogonal to the conjugation plane. Hence, no considerable spectral variation is expected during the deprotonation of $\mathbf{1H}^+$ to give $\mathbf{1}$. Further, the spectrum in this pH range is near similar to the one in methanol wherein $\mathbf{1}$ exists exclusively as species **C**. We, then conclude that the pK_a for the process, $\mathbf{1H}^{2+} \rightarrow \mathbf{1H}^+$, far below 1 in which pH range no spectra have been recorded.

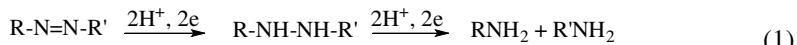
Table 1. Heats of formation, in (kJ mol⁻¹) of various conjugates of **1**.

Conjugate	Species		
	form a	form b	form c
1H₂²⁺	46.0504	48.3221	37.6557
1H⁺	0.9428	-4.1645	1.6626
1	4.1145	-0.4906	-0.5533

**Figure 2.** Heats of formation (kJ mol⁻¹) of the 3 most stable acid-conjugates of **1** (Energy of **1H₂²⁺** is reduced ten times for comparison).

Electrochemical studies

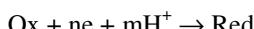
Azocompounds are known for their facile reduction of the azo moiety in aqueous media either consecutively as



or directly as



depending on the pH. Azo compounds are also known for their adsorptive and non-diffusion-controlled electrochemistry on mercury electrode¹⁶. Compound, **1**, exhibits an interesting electron transfer behavior that changes its profile with pH. The cyclic voltammetric response of **1** in some representative buffers on a stationary mercury drop electrode (SMDE) is shown in Figure 3. One observes two irreversible peaks, a broad one at a less cathodic potential and another sharp one at a higher cathodic potential with their potential gap widening with increased pH. As the pH increases, the sharp and more cathodic peak alone shifts cathodically. Coulometric studies gave the value of n involved in the adsorptive electrochemical reduction as 4. For a typical electrochemical reduction through,



the cyclic voltammetric peak potential, E_p , varies with pH as

$$E_p = E_p^0 - \frac{0.05916m}{n} \text{pH} \quad (3)$$

where E_p^0 is the peak potential at a reference pH (truly, at activity of $\text{H}^+=1$ or pH= 0). From the linear plot of E_p vs. pH, the number of H^+ ions (m) involved in the electrochemical reduction is also found as 4. Compound, **1**, offers linear i_p vs. v plots for the sharp peak at the higher cathodic potential suggesting that **1** has an adsorptive electrochemistry. The lower cathodic broad peak, however is diffusion controlled as evident from its linear i_p vs. $v^{1/2}$ plots.

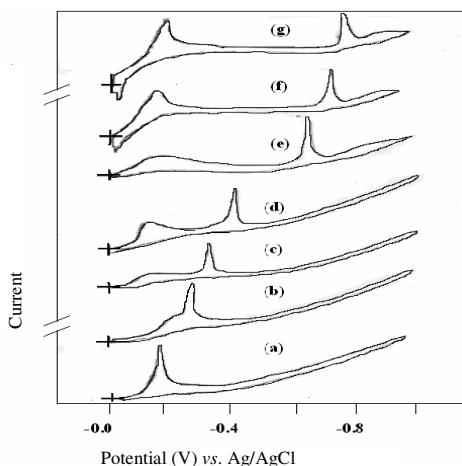
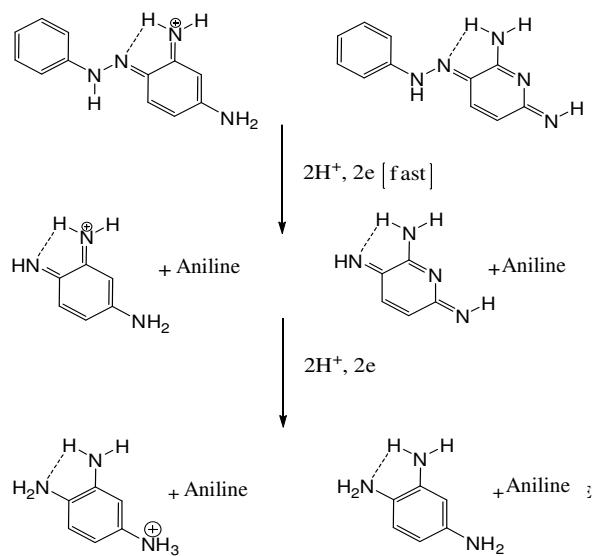


Figure 3. Cyclic voltammograms of **1** (3.5×10^{-4} M) in buffers (ionic strength = 0.05 M) of pH (a) 2.56, (b) 4.02, (c) 5.93, (d) 7.40, (e) 8.78, (f) 9.62 and (g) 10.48

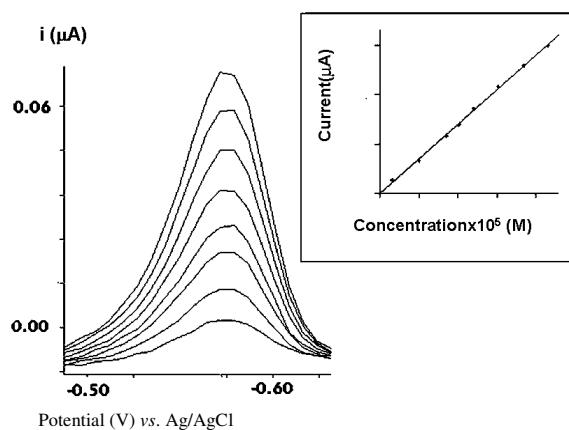
Che Man Chang has reviewed extensively the electrochemistry of aromatic azo-hydrazo redox system in aqueous media¹⁷. In general, the azo compounds undergo a two-electron and two-proton reduction at their -N=N- to end up in -NH-NH-. However, some exceptions are there. If electrochemically inactive but strong electron donating groups, such as, -OH, -NH₂ etc., interact (by resonance or hydrogen bond or tautomerically) with the azo group, the reduction may proceed directly via a four-electron step to yield the amines by reductive cleavage of -N=N- link at low pH buffers as in eqn (2) above¹⁸. It is also suggested that the electrochemical reduction of aryl amino azo compounds takes place via the quinonamine form¹⁹. In strongly acidic media, the protonated hydrazone form is predominant and is reported to undergo an electrochemical reduction without the involvement of hydrazenium/hydrazenium intermediates. We have observed from the spectral studies that an increase in pH results in a hypsochromic shift of the $n \rightarrow \pi^*$ transition Figure 1. It only means that the double bond character at the azo site as -N=N- is less at low pH than at high pH. Scheme 1 suggests how at a pH < pK_a of **1H⁺**, the analyte exists predominantly as species **B** wherein the protonated ortho hydrazone (hydrazenium cationic) form is very abundant. As pH increases its population decreases in favour of the para hydrazone (neutral) form, **C** which is more adsorptive on the electrode. In Figure 3 it can also be seen that there is a change of sorts at a pH near the pK_a below and above which the trends of E_p with pH are different. This suggests that the nature of electroactive species at pH below and that above the pK_a are slightly different. This is in line with Scheme 1. The diffusion controlled and pH-independent peak at ~ -0.2000 V is assigned to the reduction of the diffusion-controlled other forms which are present at reasonable population over the whole pH range. The plausible electrochemical reduction mechanism of compound **1** is presented in Scheme 2 for the adsorbed species. Relevant electrochemical data are collected in Table 2 for this process.

Assaying of **1**

Based on the electrochemical response of **1**, an excellent electrochemical assaying of **1**, in differential pulse polarography (DPP), is developed. The DPP curves of **1** at pH=8.00 along with the calibration curve (inset) are shown in Figure 4 (for SMDE of medium size, scan rate of 5 mVs^{-1} and pulse height of 100 mV).

**Table 2.** Voltammetric data of **1**.

pH	$-E_p$ (V) vs Ag AgCl	i_p , μA	αn_a	$D_o \times 10^6$, $\text{cm}^2 \text{s}^{-1}$	$k_{f,h}^o \times 10^9$, $\text{cm}^2 \text{s}^{-1}$
2.56	0.202	0.331	0.73	0.98	2.69
4.02	0.303	0.274	0.73	0.67	2.23
5.93	0.369	0.163	0.48	1.48	1.69
7.40	0.399	0.140	0.49	1.06	1.77
8.78	0.591	0.182	0.72	1.08	0.94
9.62	0.617	0.177	0.48	1.70	0.35
10.48	0.657	0.123	0.45	1.03	0.15

**Figure 4.** Differential pulse polarograms of **1** from $(1 \text{ to } 8) \times 10^{-5}$ M.

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