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Registry No.—SbF_5, 7783-70-2; propane, 74-98-6; *n*-butane, 106-97-8; isobutane, 75-28-5; hexane, 110-54-3; cyclohexane, 110-82-7.

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Mechanism of the Oxidative Cyclization of *N'*-(*p*-Hydroxyphenyl)-2-(phenylamino)-5-methyl-*p*-benzoquinone Diimine in Aqueous Solution

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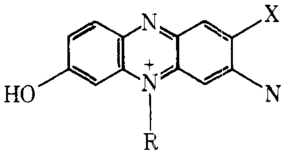
The title compound undergoes intramolecular cyclization in aqueous solution to give a quantitative yield of 2-amino-8-hydroxy-3-methyl-10-phenylphenazinium salt. In the absence of any other oxidant, the rate-controlling step between pH 8 and 12 is aerial oxidation of the intermediate 2-amino-8-hydroxy-3-methyl-10-phenyl-5,10-dihydrophenazine to the product, whereas outside this pH range the cyclization step is rate controlling.

In a recent publication,[1] we proposed a mechanism for formation of 2-amino-8-hydroxyphenazines (**1**) from *N'*-(*p*-hydroxyphenyl)-2-amino-*p*-benzoquinone diimines (**2**).



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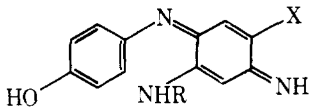

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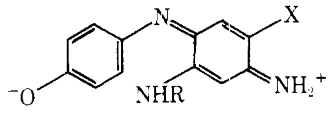

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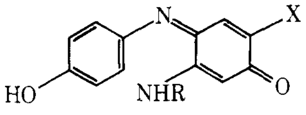

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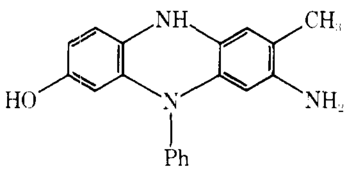

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We were unable to study the 2-*N*-phenyl diimine (**2**, X = Me, R = Ph) above pH 8.5 due to the rapid reaction rate, but over the pH range 6–8 only data consistent with the proposed mechanism were obtained. We have now extended the study of this diimine to cover the full pH range and have found anomalous results at pH > 8 which lead us to a more detailed mechanism for the cyclization reaction.

Results and Discussion

Spectra and Products. At pH > 10, the title diimine rapidly converted to the phenazine. Therefore, spectral data of the diimine at high pH were difficult to obtain. At lower pH the diimine was considerably more stable and two ionic forms were observed: a red cation (λ 518 nm) and a blue zwitterion (λ 675 nm). By rapidly injecting diimine into buffers of different pH and then scanning a selected part of the visible spectrum, the pK_a was estimated as 8. Using this same technique, the diimine anion was shown to be red with a pK_a around 12 (estimated at 650 nm since phenazine formation is relatively slow up to pH 12 and its spectrum does not interfere at this wavelength). These data are consistent with those of previously reported analogues. The high reactivity of the diimine precludes further structural characterization.

Over the pH range 5–13, the diimine cyclized quantitatively to the phenazinium salt (**1**, R = Ph, X = Me). The phenazine spectrum has been described previously[2] and shows a zwitterion [λ 513 nm (log ϵ 4.48), pK_a 5.4] at high pH and a cation [λ 498 nm (log ϵ 4.25) and 436 (4.16)] at lower pH.

Kinetics of Cyclization. Unlike with analogous diimines, the spectrophotometric course of the cyclization reaction was not simple. Between pH 8 and 12, scans of the visible spectrum of a reacting solution showed no isosbestic point, and loss of the spectrum of the diimine was considerably faster than appearance of phenazine. Kinetic analysis showed that both imine loss and phenazine formation followed first-order kinetics but that derived rate constants could be as much as a factor of 50 apart depending on the solution pH. Below pH 7.5, the spectrophotometric scans showed a clean isosbestic point and the rate constant was independent of wavelength. As the pH was raised, the rate of loss of imine increased dramatically so that the half-life was only a few seconds at pH 12. However, the rate of phenazine formation changed little over this pH range, only beginning to increase noticeably above pH 12. First-order rate constants for loss of imine (k') and phenazine formation (k'') are given in Table I.

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Table I. Phenazine Yield and Rate Constants for Cyclization of Diimine at 30 °C

pH	% phenazine	$10^2k'$,[a] s^{-1}	$10^2k''$,[a] s^{-1}
5.21	100		0.0041
5.98	103		0.032
6.61	110	0.112	0.103
7.04	110	0.193	0.277
7.53	107	0.55	0.260
8.22	103	1.16	0.075
8.57	99	1.51	
8.79	103	1.44	
9.02	91	1.72	0.060
9.08	101		0.036
9.10	105	1.78	
9.48	98	2.49	
10.12	92		0.15
10.21	98	2.57	
10.62	107	3.96	
11.05	97	7.29	
11.47	93	8.66	0.13
11.80	96		0.52
12.00	99	11.55	
12.22	108		2.77
13.30	101		19.80

[a] k' is evaluated from loss of imine peak at 650 nm. k'' is evaluated from formation of phenazine peak at 513 nm.

We previously proposed[1] that analogous diimines cyclize through the zwitterionic form **3**, and the rate of cyclization at any pH was given by eq i, where α is the fraction of diimine as

$$-\mathrm{d}[\text{diimine}]/\mathrm{d}t = k^0[\text{zwitterion}] = k\alpha[\text{diimine}] \qquad \text{(i)}$$

zwitterion at the pH to which k^0 pertains and k is the specific first-order rate constant for zwitterion cyclization. The present diimine also follows this equation up to pH 10, and k is evaluated as 0.023 ± 0.004 s^{-1}.

Above pH 10, eq i predicts that the rate of cyclization should decrease as zwitterion is converted to the unreactive anion. This was observed with the 2-*N*-methyl diimine (**2**, R = X = Me) between pH 10 and 12. However, other analogues (**2**, R = H, X = H or Me) showed an increase in rate with pH over this range due to the formation of a second product, 2-aminoindophenol (**4**). Neither pattern was followed by the *N*-phenyl diimine. Although only the corresponding phenazine was formed up to pH 13, the rate of cyclization did not follow the concentration of zwitterion but increased rapidly with solution pH. Thus, above pH 10, either the diimine anion cyclizes or the zwitterion interacts with hydroxide ion. These two reactions are kinetically indistinguishable. Specific rate constants for these reactions are evaluated from the relationships shown in eq ii and iii, where k and α have their

$$k' = k_A\alpha_A + k\alpha \qquad \text{(ii)}$$

$$k' = k_2\alpha[\text{OH}^-] + k\alpha \qquad \text{(iii)}$$

previous significance, k' is the experimental rate constant, α_A is the fraction of diimine as anion at the pH where k' was determined, k_A is the specific first-order rate constant for anion cyclization, and k_2 is the specific second-order rate constant for zwitterion reacting with hydroxide ion. Using the data of Table I, k_A was evaluated as 0.33 s^{-1} and k_2 as 30 L mol^{-1} s^{-1}.

We are unable to offer any suggestions for a reaction of zwitterion with hydroxide ion that would lead to phenazine. Moreover, while we expect the anion to cyclize more quickly when R = Ph than for R = Me or H, we cannot explain the faster rate of cyclization of the anion as compared to the zwitterion in the present case. Indeed for the 2-*N*-methyl analogue (**2**, R = Me), all cyclization resulted from the zwitterion even when the anion was the majority species in solution. Thus, the mechanism of the reaction at pH > 10 is not clear at this time. However, using either eq ii or iii, rate constant k' can be evaluated at any pH using k = 0.023 s^{-1}, k_A = 0.33 s^{-1}, and k_2 = 30 L mol^{-1} s^{-1}. The variation of calculated values of k' with pH is shown in Figure 1 as the solid line, and the experimental values of k' are superimposed (open circles). The agreement between calculation and theory is good even in the pH range 10–11, where the two reactions occur.

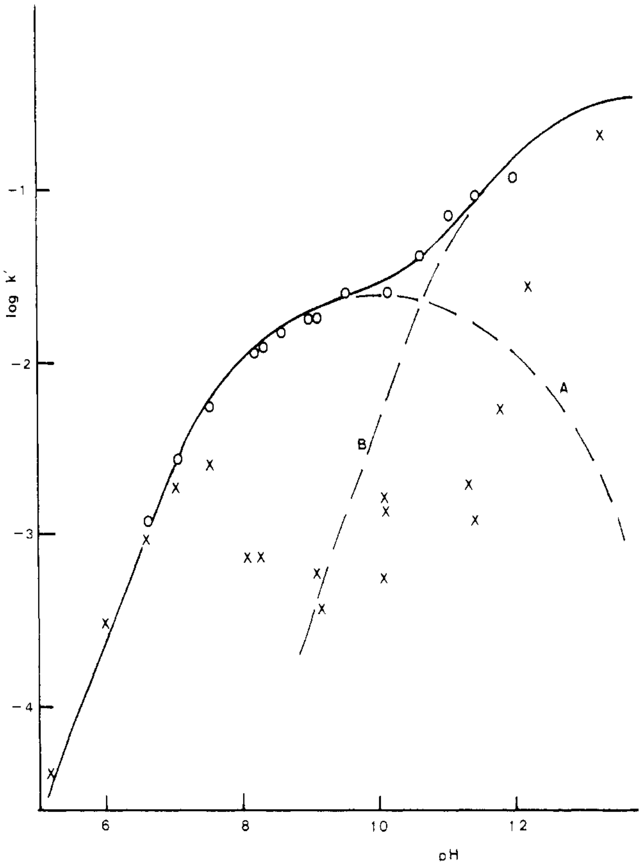
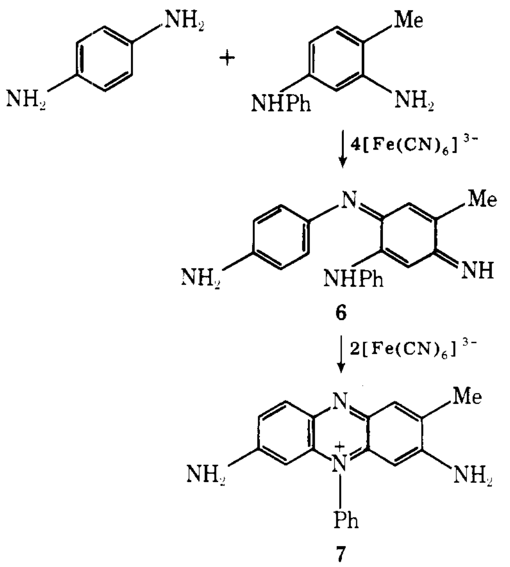


Figure 1. Variation of log k' with pH for cyclization of diimine (**2**, R = Ph, X = Me) at 30 °C. Circles are experimental values for diimine disappearance, and crosses are the rate of phenazine formation. The solid line is calculated from eq ii, and the dotted lines represent individual contributions from (A) zwitterion cyclization and (B) the hydroxide ion and zwitterion reaction, or anion cyclization.

Mechanism of Cyclization. It is clear from kinetic data that phenazine is formed at a considerably slower rate than imine disappears from solution, suggesting that an intermediate is involved in the reaction. We now present evidence that this intermediate is the N^{10}-phenyl-5,10-dihydrophenazine derivative **5**, which is only slowly oxidized to the reaction product (**1**, R = Ph, X = Me) by dissolved oxygen.

At pH 8.2, the half-lives for imine decomposition and phenazine formation are about 60 and 1000 s, respectively. A solution of diimine was prepared at pH 8.2, and after 5 min (98% reaction of diimine) 2 molar equiv of potassium ferricyanide was added. The half-life for phenazine formation was now 14 s (rate constant 0.05 s^{-1}), and a quantitative yield of phenazine was formed within 2 min. Thus, when ferricyanide is added, the rate of phenazine formation is rapid compared to the cyclization reaction. However, even under these conditions, phenazine formation is not a particularly fast reaction, suggesting that the oxidation is relatively difficult. A similar reaction under anaerobic conditions gave the same first-order rate constant for diimine disappearance (0.0117 s^{-1}) but showed essentially no phenazine formation. With the addition

Scheme I. Formation and Cyclization of 2-(Phenylamino)-5-methylindamine



of successive amounts of ferricyanide to the solution, phenazine formation increased rapidly and in stepwise fashion, until the addition of further ferricyanide gave no increase in the phenazine yield. However, since ferricyanide was shown to react with diimine to give products other than phenazine, the kinetic form of the reaction could not be simplified by carrying out diimine cyclizations in the presence of excess ferricyanide.

Thus, the rate difference between imine loss and phenazine formation is due to a slow oxidation by dissolved oxygen of the phenazine precursor. This reaction is essentially independent of pH and somewhat nonreproducible (Figure 1, crosses). It is interesting to note that there is a rapid increase in this oxidation rate above pH 11.5, which coincides with the increased importance of the reaction between imine zwitterion and hydroxide ion. The reason for this is not clear and will require further study.

Scheme II. Mechanism for Oxidative Cyclization of Diimine Zwitterion

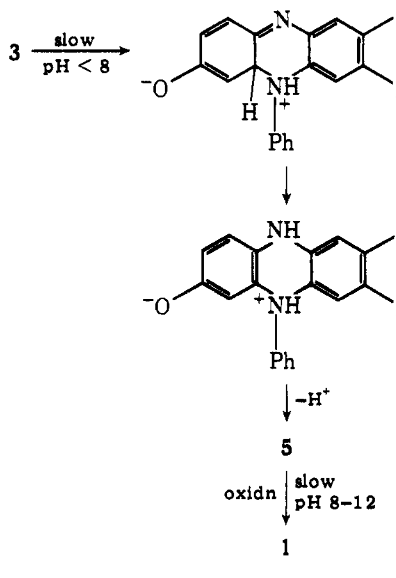


Table II. Rate Data for the Formation of Phenazinium Salt (7) at pH 7.0 and 30 °C

10^5[PPD],[a] mol/L	10^5[FC], mol/L	10^3k_L (loss of imine), s^{-1}	10^3k_F (formation of phenazine), s^{-1}
5.0	10.0	3.38	0.264
5.0	20.0	3.01	2.58
5.0	40.0	2.53	2.64[b]

[a] Excess diphenylamine used. [b] Published value:[3] $k_F = 2.20 \times 10^{-3}$ s^{-1} at 30 °C at [PPD] = 5×10^{-5} M, [FC] = 30×10^{-5} M.

Because of these surprising results, we have reexamined the formation of 3-methyl-10-phenyl-2,8-diaminophenazinium salt (**7**) from *p*-phenylenediamine and 3-amino-4-methyldiphenylamine. Previous work[3] showed that this reaction occurred through the indamine (**6**), and 6 equiv of potassium ferricyanide was required to complete the reaction (Scheme I). Since this reaction involves similar chemistry to the current work, we examined the reaction kinetics with less than 6 equiv of ferricyanide added. Table II shows that the rate of phenazine formation was reduced dramatically, whereas the loss of imine increased slightly.[6] In addition, at the lower ferricyanide concentrations, no isosbestic point was observed in repetitive scans of the visible spectra of reacting solutions. These results are clearly similar to those obtained with the present system, suggesting the generality of the results.

Thus, it appears that dissolved oxygen, which usually acts as a kinetically fast oxidant for dihydrophenazines,[4] has a limiting oxidation rate, at least for N^{10}-phenyldihydrophenazines, of about 10^{-3} s^{-1}. Where cyclization rates are significantly faster than 10^{-3} s^{-1}, the oxidation becomes the rate-controlling step.

The overall mechanism for cyclization of these diimines is therefore shown in Scheme II. The reaction of zwitterion with hydroxide ion and the effect of hydroxide ion on the dihydrophenazine oxidation are, however, not shown. Thus, we have been able to confirm some aspects of the mechanism that we proposed previously and to expand on specific steps.

Experimental Section

Materials. *N'*-(*p*-Hydroxyphenyl)-2-(phenylamino)-5-methyl-*p*-benzoquinone diimine (**2**, X = Me, R = Ph) was prepared by the previously described technique, except that potassium ferricyanide was used as oxidant. The violet precipitate, mp 280 ° C dec, was a ferricyanide salt of the above imine and was difficult to obtain in a pure state due to the ease with which it converted to the phenazine.

2-Amino-8-hydroxy-3-methyl-10-phenylphenazinium salt was prepared by dissolving the above diimine in pH 10 buffer and collecting the precipitate after a few hours. Found: C, 75.0; H, 5.7; N, 13.5; O, 5.8. $C_{19}H_{16}N_3O$ requires C, 75.7, H, 5.1, N, 13.9, and O, 5.3. An authentic sample of this phenazine was prepared by Jaubert's method.[5] It was chromatographically and spectrally identical with the above sample [zwitterion, λ 513 nm (log ε 4.48), pK_a 5.4; cation, λ 498 nm (log ε 4.28) and 436 (4.14)].

Kinetics. An aliquot of diimine solution was injected into a thermally equilibrated buffer solution. Reactions were followed by scanning the visible spectrum of the solution at various times using a Unicam SP 800 A spectrophotometer. For faster reactions, the spectrum was scanned at a single wavelength. Rate constants were evaluated from these scans by standard techniques. Product yields were determined from scans taken after ten first-order half-lives. Ionization constants were determined spectrophotometrically.

Registry No.—**1** (R = Ph, X = Me), 68225-89-8; **2** (R = Ph, X = Me), 68225-90-1; **7**, 68225-91-2; *p*-phenylenediamine, 106-50-3; 3-amino-4-methyldiphenylamine, 6406-71-9.

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