Benzoquinone Imines. Part 15.[1] Kinetics and Mechanism of the Hydrolysis and Cyclization of 2-Amino-*N*-(*p*-hydroxyphenyl)-*p*-benzoquinone Di-imines in Aqueous Solution

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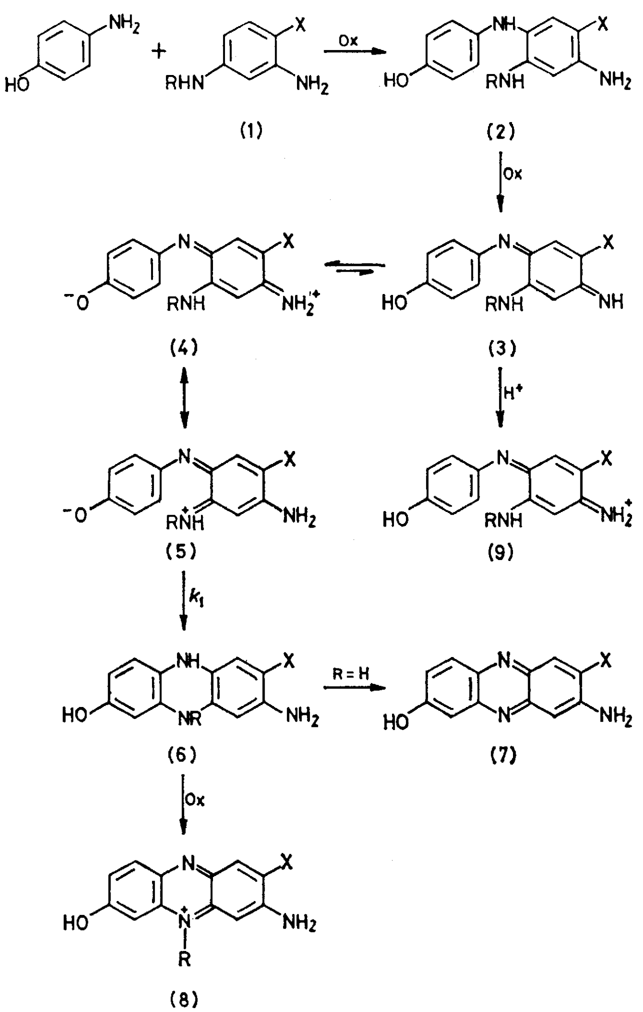
2-Amino-*N*'-(*p*-hydroxyphenyl)-*p*-benzoquinone di-imines undergo hydrolysis at the azomethine bridge at pH <4, intramolecular cyclization to 2-amino-8-hydroxyphenazines at pH 6—10, and hydrolysis at the terminal imino-group at higher pH. Acid hydrolysis involves reaction of the dication with water forming *p*-aminophenol and 2-amino-*p*-benzoquinone monoimine. Phenazine formation occurs by intramolecular coupling of the 2-amino-nitrogen of the zwitterion to the 2'-carbon atom, followed by oxidation. Alkaline hydrolysis involves attack by hydroxide ion on the zwitterion to give the corresponding 2-aminoindophenol.



SCHEME 1 Formation and oxidative cyclization of the di-imines (3)

IN 1895, Nietzki and Simon[2] showed that oxidation of 2,4-diamino-4'-hydroxydiphenylamine (2; R = X = H) with manganese dioxide in hot aqueous ammoniacal solution gave 2-amino-8-hydroxyphenazine (7; X = H). It was later found[3] that similar treatment of a mixture of *p*-aminophenol and 2,4-diaminotoluene gave an analogous phenazine (7; X = Me). By working with cold solutions of *p*-aminophenol and *m*-phenylenediamine, Ullmann and Gnaedinger[4] were able to isolate the intermediate (3; R = X = H), the constitution of which was confirmed by reduction to the diphenylamine (2; R = X = H), and by oxidation to the phenazine with air in hot ammoniacal solution. The 10-methyl derivative of the phenazine (8; R = X = Me) was prepared by condensation and oxidation of a mixture of *p*-nitrosophenol and 2-amino-4-methylaminotoluene (1; R = X = Me), with manganese dioxide in dilute acid.[5]

We have previously deduced the mechanism for oxidative coupling of *p*-aminophenols with *m*-phenylenediamines to give the di-imines (3).[6] We now present data supporting a mechanism for the intramolecular cyclization of these imines to give aminohydroxyphenazines (7) and (8).

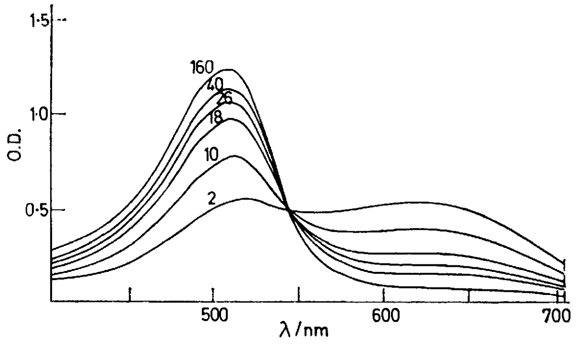


FIGURE 1 Spectrophotometric course of the cyclization of the dye (3; R = X = Me) to the phenazinium salt (8; R = X = Me) at pH 11.0 and 30 °C. Times given in minutes

Over the pH range 0—14, the title compounds exist in three ionic forms, a red cationic species (9) having a $\mathrm{p}K_a$ *ca.* 8, a blue zwitterion (4) having a $\mathrm{p}K_a$ *ca.* 12, and a red anionic species (15). Spectral data for the compounds studied are given in Table 1.

Preliminary experiments showed that the di-imine (3; R = X = Me) is most stable in the pH range 3—7. In the pH range 7.5—12, the blue dye undergoes intramolecular cyclization to give a quantitative yield of the corresponding phenazinium salt (8; R = X = Me). The kinetics of the reaction were obtained spectrophotometrically (Figure 1). At constant pH, the reaction follows the first-order rate law and the rate increases *ca.* ten-fold between pH 7 and 8; the rate of increasing rate with increasing pH becoming less above pH 8. Maximal rate is attained at pH 10.2 whereafter the rate decreases with increasing pH. These results are consistent with a rate-controlling step involving intramolecular cyclization of the zwitterionic form (4; R = X = Me) probably *via* electrophilic attack of the iminium group of form (5) on the carbon atom *ortho* to the azomethine bridge, to give the leucophenazine (6; R = X = Me) which undergoes rapid oxidation to the phenazinium salt (8; R = X = Me) (Scheme 1). The rate of cyclization is given by equation (1) where k is the

$$k = k_1 \alpha \qquad (1)$$

observed rate constant, k_1 is the specific first-order rate constant for the intramolecular cyclization of the zwitterion, and α is the fraction of dye present as the zwitterionic form at the pH to which k pertains. From data in Table 2, k_1 was found to be 1.36×10^{-3} s^{-1}.

TABLE 1

Spectra of the di-imines (3) in aqueous solution

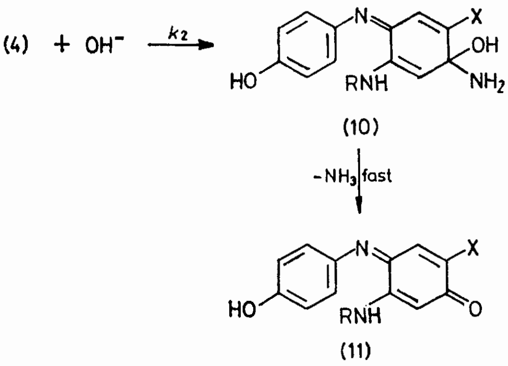
Dye (3)		λ_{max} (log ε) and pK_a				
R	X	Monocation (9)	pK_a	Zwitterion (4)	pK_a	Anion (15)
H	H	490 (4.12)	8.1	628 (4.46)	11.7	510 (4.14)
H	Me	492 (4.07)	8.3	624 (4.36)	11.8	504 (4.07)
Me	Me	495 (4.05)	8.3	618 (4.27)	12.1	494 (4.13)
Ph	Me	518 (*)	~8	675 (*)	~12	*

* Rapid formation of phenazine from this di-imine does not allow accurate determination of these values.

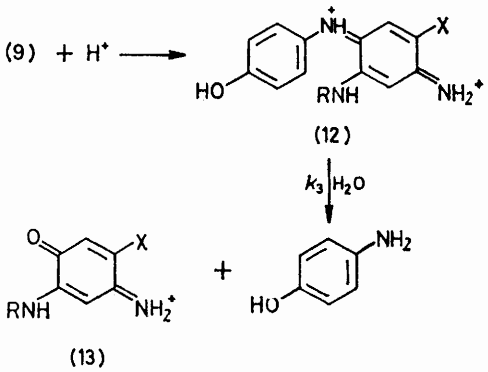
The parent dye (3; R = X = H) and its 5-methyl derivative (3; R = H, X = Me) behave similarly over the pH range 7—10 but the cyclization is considerably slower ($k_1 = 8.4 \times 10^{-5}$ and 7.0×10^{-5} s^{-1} respectively). Furthermore, above pH 10, the rate of disappearance of the indo-dye increases with increasing pH, the yield of phenazine decreases, and a second product is apparent. This second product was shown to be the corresponding 2-aminoindophenol (11; X = Me, R = H) which can be obtained by oxidative coupling of *p*-aminophenol with 5-amino-2-methylphenol.[1] The formation of (11) results from hydrolysis of the terminal imino-group of (4). It was shown previously [7] that 2-aminoindamines undergo a similar hydrolysis at high pH and that the mechanism involves attack by hydroxide ion on the carbon atom of the iminium group. Assuming a similar mechanism for the present case and that the zwitterion is the reactive form, the rate constant for disappearance of the indo-dyes, k, is given by equation (2), where k_1, and α are the same as in equation (1), and k_2 is the specific second-order rate constant for hydrolysis of the iminium group.

$$k = k_1 \alpha + k_2 \alpha [\mathrm{OH}^-] \qquad (2)$$

Since k_1 and α are known, k_2 can be calculated from equation (2) for values of k at various pH. The results for (3; R = H, X = Me) are given in Table 3, from which we get $k_2 = 0.024$ l mol^{-1} s^{-1}. Similar experiments with the parent dye (3; R = X = H) give $k_2 = 0.013$ l mol^{-1} s^{-1}. This supports the mechanism shown in Scheme 2.



SCHEME 2 Hydrolysis of di-imines (4) in alkaline solution



SCHEME 3 Hydrolysis of di-imines in acid solution

There was no evidence for similar hydrolysis of (3; R = X = Me) up to pH 12, but at pH 12.4 the yield of phenazinium salt is *ca.* 90% while, at pH 14, it is only 20%. From rate data at pH 12.3 and 14.0 we estimate the hydrolysis rate constant k_2 to be 5×10^{-3} l mol^{-1} s^{-1}. The 2-anilino-di-imine (3; R = Ph, X = Me) showed qualitatively similar behaviour to the methyl analogue (3; R = X = Me) except that cyclization to phenazinium salt (8; R = Ph, X = Me) was much faster. Therefore, it was only practical to study the cyclization from pH 6 to 8.5. In this range, quantitative yields of phenazine were formed, and k_1 was evaluated as 2.3×10^{-2} s^{-1}.

TABLE 2

Rate data for the cyclization of dye (3; R = X = Me) in aqueous solution at 30 °C

pH	% Phenazine	10^4k/s^{-1}	10^3k_1/s^{-1}
6.95	~100	0.72	1.50
8.16	~100	6.24	1.56
9.10	~100	11.0	1.28
10.2	97	12.8	1.30
11.4	97	10.5	1.26
11.9	96	8.68	1.42
12.3	~90	5.25	(1.21) *
14.0	~20	0.77	(1.33) *
		Mean:	1.36 ± 0.12

* After correction for yield of phenazine.

At pH values below 3.5, the major reaction of the indo-dyes (3) is hydrolysis at the azomethine bridge to give a mixture of *p*-aminophenol and the appropriate 2-amino-*p*-benzoquinone monoimine (13). In addition a small, but relatively constant proportion (5—10%) of the phenazine is formed. Over the pH range 1—3.5, the rate of disappearance of the indo-dye follows first-order rate law and the rate constant decreases ten-fold for each unit increase in pH. Since the dye (3) exists as the monocation (9) in this pH range, it is concluded that the reactions involve a minority species—the dication (12). Reaction of (12) with water results in hydrolytic fission, while intramolecular cyclization of (12) gives rise to the phenazine (7) or (8). Rate data for these reactions at constant ionic strength (1M-NaCl) are given in Table 4. The rate constant for disappearance of the dye (3) is given by equation (3) where k_1' relates to cyclization, k_3 to hydrolysis, and α' is the fraction of the dye (3) present as the monocation at the pH to which k pertains.

$$k = k_1'\,\alpha'[H^+] + k_3\,\alpha'[H^+] \qquad (3)$$

TABLE 3

Rate data for cyclization and alkaline hydrolysis of the dye (3; R = H, X = Me) in aqueous solution at 30 °C

pH	% Phenazine	$10^5k/s^{-1}$	$10^4k_1\alpha/s^{-1}$ *	10^2k_2 †
9.09	~100	5.55	6.03	
9.71	~100	6.58	6.67	
10.2	~100	7.19	6.74	(2.95) ‡
10.9	67	7.60	6.21	(1.97) ‡
11.0	61	8.14	6.04	2.49
11.1	65	8.73	5.84	2.72
11.4	59	9.30	5.01	2.40
11.7	46	10.9	3.90	2.52
11.8	39	10.2	3.50	2.23
11.9	28	11.7	3.10	2.29
12.3	12	14.4	1.68	2.65
14.0	0	14.2	0.004	2.25
			Mean:	2.45 ±0.28

* Calculated using $k_1 = 7.0 \times 10^{-5}\ s^{-1}$. † Calculated from equation (2). ‡ Inaccurate due to small difference $10^5k - 10^4k_1\alpha$.

TABLE 4

Rate data for reactions of the dyes (3) in aqueous solution at pH 1—3.5 and 30 °C

Dye (3) R	X	pH	$10^4k/s^{-1}$	% Phenazine	$10^3k_1'$ †	10^2k_3 *
H	H	0.96	37.5	8	2.7	3.14
		1.72	6.19	5	1.8	3.35
		2.50	1.03	10	3.2	2.93
				Mean:	2.6	3.14
H	Me	1.12	31.1	4	3.4	3.93
		1.66	9.1	8	3.3	3.82
		1.84	6.1	10	4.2	3.76
		1.94	4.1	9	3.2	3.24
		2.51	1.3	9	3.8	3.82
				Mean:	3.6	3.71
Me	Me	1.00	26.3	7	1.8	2.45
		1.38	11.1	2	0.5	2.61
		1.50	8.4	7	1.8	2.47
		2.00	2.7	5	1.4	2.57
		2.89	0.33	7	1.8	2.38
		3.33	0.13	2	0.6	2.71
				Mean:	1.3	2.53

* Calculated from $k_3 = k \times (100 - \%\ \text{Phenazine})/(100[H^+])$. † Calculated from $k_1' = k \times (\%\ \text{Phenazine})/(100[H^+])$.

Since the pK_a of the reactive species is not known, it is not possible to comment on the effect of the substituents on these rates or upon the relative rate of cyclization of the dication compared with the zwitterion.

From the present work it is evident that, over the pH range 1—14, the di-imines (3) undergo reactions to give three products. The disappearance of the dye (3) at any pH follows first-order kinetics and the rate constant k is

$$k = k_1'\,\alpha'[H^+] + k_3\,\alpha'[H^+] + k_1\,\alpha + k_2\,\alpha[OH^-] \quad (4)$$

given by a combination (4) of equations (2) and (3), where the k's and α's have their previous significance.

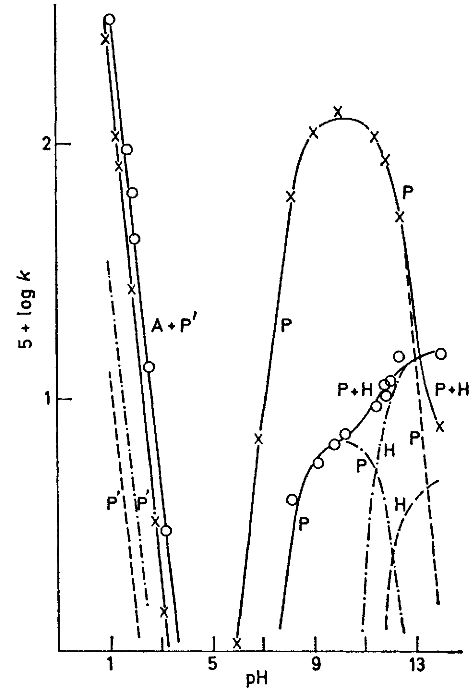


FIGURE 2 Experimental points for the reactions of the dyes (3; R = H, X = Me) = ○ and (3; R = X = Me) = ×, and the theoretical curves (—) from equation (4). The contributions of $k_1'\alpha[H^+]$ labelled P', $k_1\alpha$ labelled P, and $k_2\alpha[OH^-]$ labelled H are shown as broken lines for (3; R = X = Me) and as broken dotted lines for (3; R = H, X = Me). The contributions of $k_3\alpha'$ [H⁺] for acid hydrolysis labelled A are almost coincident with the full lines (A + P') and are not shown separately

TABLE 5

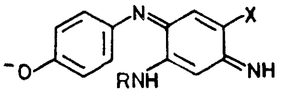
Comparison of the rate constants for the intramolecular cyclization of the dyes (3) with those for analogous 2-aminoindamines at 30 °C

Indo-dyes (3) and (14) R	X	Rate constants (k_1/s^{-1}) (3)	(14) *	Ratio (3)/(14)
H	H	8.4×10^{-5}	6.1×10^{-6}	13.8
H	Me	7.0×10^{-5}	2.7×10^{-6}	25.9
Me	Me	1.36×10^{-3}	1.4×10^{-5}	97.1
Ph	Me	2.30×10^{-2}	2.2×10^{-3}	10.5

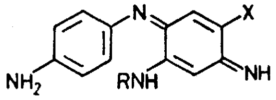
* Data from references 7—9.

Figure 2 shows the good fit of experimental points to the theoretical line calculated from equation (4) for reactions of dyes (3; R = X = Me) and (3; R = H, X = Me). From the curves, it is evident that the optimum pH for phenazine formation is in the region 9—10.

It is of interest to compare the rates of intramolecular cyclization of the di-imines (3) with those for the analogous 2-aminoindamines (14). The former involves attack by an iminium group on a carbon *meta* to a phenoxide group, while the latter involves similar attack on a carbon *meta* to an amino-group.[8,9] From Table 5 it is evident that the dyes (3) cyclize 10—100 times faster than their indamine analogues. It is noteworthy that, in coupling reactions with the *p*-benzoquinone di-iminium ion, the *para*-position of the phenoxide[10] ion is 2.5 × 10^4 times more reactive than the *para*-position of aniline.[11]



(15)



(14)

TABLE 6

Spectra of products from dyes (3) in aqueous solution

	$\lambda_{max.}$ (log ε)				
	Cation	pK_a	Neutral	pK_a	Anion
Phenazines					
(7; X = H)	430 (4.16); 488 (4.23)	4.3	406 (4.09); 490 (4.17)	8.0	437 (4.27)
(7; X = Me)	435 (4.20); 483 (4.20)	4.7	409 (4.09); 494 (4.10)	8.3	437 (4.29)
(8; R = X = Me)	434 (4.29); 490 (4.35)	5.1	509 (4.58)		*
(8; R = Ph, X = Me)	436 (4.16); 498 (4.25)	5.4	513 (4.48)		*
2-Aminoindophenols					
(11; R = X = H)			470 (3.90)	8.9	572 (4.24)
(11; R = H, X = Me)			464 (3.88)	9.0	556 (4.22)
2-Amino-*p*-quinone imines					
(13; R = X = H)	~409				
(13; R = H, X = Me)	508 (3.66)				
(13; R = X = Me)	512 (3.76)				

* No anionic form.

The activation energy for phenazine formation is 20.4 kcal mol^{-1} which agrees well with the value of 24.5 kcal mol^{-1} for 2-aminoindamine cyclization.[8]

Table 6 gives spectral data for the products of the various reactions of the dyes (3). The phenazines have relatively complex spectra which will be discussed in a later publication.

EXPERIMENTAL

Materials.—*p*-Aminophenol, the *m*-diamines (1; R = H), the imine (3; R = H, X = Me), and 2-amino-8-hydroxy-3-methylphenazine were commercial samples. The *m*-diamine (1; R = X = Me) was prepared by catalytic reduction of 2-nitro-4-methylaminotoluene,[12] and the *m*-diamine (1; R = Ph, X = Me) by catalytic reduction of 3-nitro-4-methyldiphenylamine.[9] The 2-aminoindophenols (11; X = H or Me) have been described previously,[1] as have the 2-amino-*p*-benzoquinone-4-imines,[7,8] 2-amino-*N'*(*p*-hydroxyphenyl)-*p*-benzoquinone di-imine,[6] and 2-amino-8-hydroxyphenazine.[2] The remaining di-imines and phenazines were prepared by adapting the following techniques:

*2-Methylamino-5-methyl-*N'-(p-*hydroxyphenyl*)-p-*benzoquinone Di-imine.*—To an aqueous solution (20 ml) of *p*-aminophenol hydrochloride (0.72 g) and 2-amino-4-methylaminotoluene hydrochloride (1.03 g) was added hydrogen peroxide (6%, 10 ml) and ammonia (2.5 ml). Dark red needles, m.p. 169—171 °C, of the di-imine monohydrate were obtained (Found: C, 64.0; H, 6.2; N, 16.1%. $C_{14}H_{15}N_3O{\cdot}H_2O$ requires C, 64.8; H, 6.5; N, 16.2%).

*2-Amino-8-hydroxy-*3,10-*dimethylphenazinium Salt.*—The above di-imine (0.1 g) was dissolved in carbonate buffer (pH 10; 50 ml). After 24 h, dark red plates, m.p. 130 °C (decomp.), of the phenazinium hydroxide were collected (Found: C, 64.9; H, 5.2; N, 16.0. $C_{14}H_{14}N_3O{\cdot}OH$ requires C, 65.2; H, 5.9; N, 16.3%).

Kinetics.—Reaction rates were determined spectrophotometrically, using a Unicam SP 800A spectrophotometer, by repetitively scanning the visible spectrum (for slow reactions) or recording optical density at constant wavelength (for fast reactions). Ionization constants and spectra of di-imines and phenazines were determined by standard techniques.

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