Benzoquinone Imines. Part 17.[1] Kinetics and Mechanism of the Hydrolysis and Cyclization of 2-Aminoindophenols in Aqueous Solution

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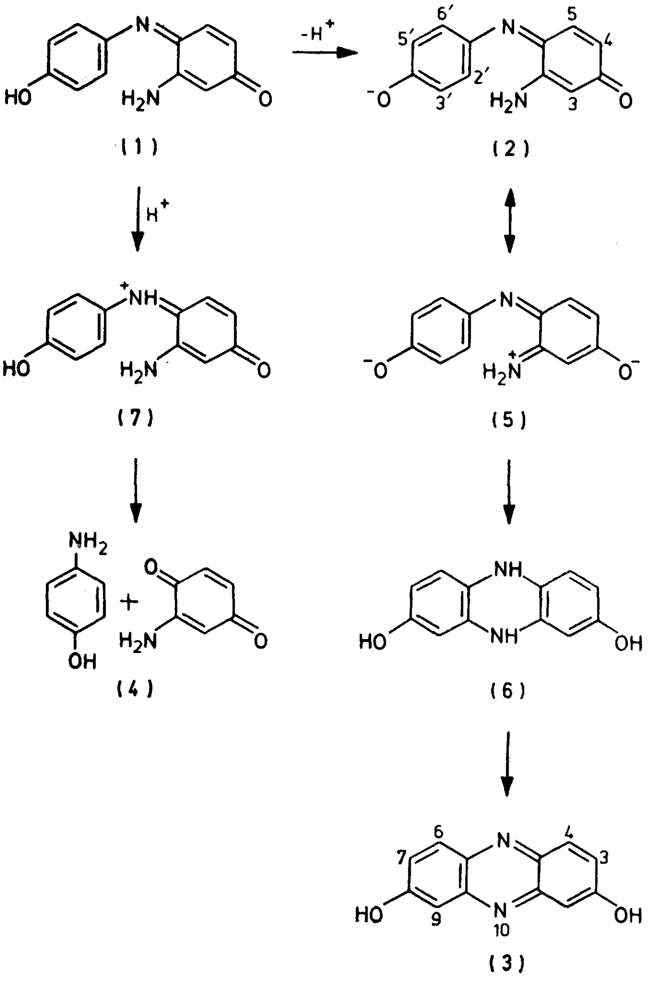
2-Aminoindophenols undergo hydrolysis at the azomethine bridge at pH < 5 and intramolecular cyclization, to give 2,8-dihydroxyphenazines, at pH > 8. At intermediate pH, decomposition occurs to give products which have not been identified. Phenazine formation involves the indophenol anion and hydrolysis the monocation. The neutral species is relatively stable. The instability of the anion towards oxidizing agents, including hydrogen peroxide formed in the air oxidation of the dihydrophenazine, mitigates against the use of the reaction for preparative purposes.

WE have previously studied[2] the formation of aminoindophenols by the oxidative coupling of *p*-aminophenols with *m*-aminophenols. It was found that the reaction involved electrophilic attack by neutral (pH > 11) and conjugate acid (pH 7—9) of *p*-benzoquinone monoimine at the 4-position of the 3-aminophenolate ion to give the corresponding 2-amino-4,4′-dihydroxydiphenylamine which is rapidly oxidized to the 2-aminoindophenol (1). The rate of formation of (1) is *ca.* 100-fold higher at pH 12 than at pH 8. We have now extended the work to the examination of reactions of the 2-aminoindophenols in aqueous solution.



SCHEME

Spectral data for some 2-aminoindophenols have been published previously,[2] others are given in Table 1. At pH > 10 the dyes exist as the blue anionic form (2) and at lower pH values the red neutral form (1) is the major species. The effect of methyl and chloro-substitution on the spectra is similar to that observed for simple indophenols.[3] Thus methyl substitution on the benzenoid ring and chloro-substitution on the quinonoid ring result in small bathochromic shifts while methyl substitution on the quinonoid ring and chloro-substitution on the benzenoid ring result in hypsochromic shifts.

When the blue solution of the 2-aminoindophenolate ion is heated, it slowly becomes red due to the formation of the corresponding 2,8-dihydroxyphenazine (3). Neutral solutions of the indo-dye are considerably more stable and, while the colour fades slowly, we have not been able to identify any coloured decomposition products. At lower pH, *i.e.* 0—5, the dye is again unstable owing to hydrolysis at the azomethine bridge to give the corresponding *p*-aminophenol, which was identified chromatographically, and 2-amino-*p*-benzoquinone (4) which was identified spectrophotometrically and by acid hydrolysis to 2-hydroxy-*p*-benzoquinone which can be isolated by steam distillation.

Some initial difficulties were encountered in establishing a technique to follow the kinetics of the cyclization reaction spectrophotometrically. First, since we had been unable to isolate many of the indophenols, it was necessary to prepare them *in situ*. Further, the slow conversion into phenazine at 30 °C required studying the kinetics at higher temperatures. While we had found previously[2] that quantitative yields of the indophenol could be obtained at 30 °C either by air or potassium ferricyanide oxidation of mixtures of the *p*- and *m*-aminophenols, yields at higher temperatures were low owing to the destruction of the *m*-aminophenol by ferricyanide or by hydrogen peroxide formed by air oxidation of the *p*-aminophenol [reaction (1)].

$$p\text{-aminophenol} + O_2 \longrightarrow p\text{-benzoquinone monoimine} + H_2O_2 \quad (1)$$

It was also found that hydrogen peroxide reacted rapidly with the 2-aminoindophenols (1) at elevated

TABLE 1

Spectra and dissociation constants of 2-aminoindophenols (2)

3′-Substituent	2′-Substituent	4-Substituent	3-Substituent	Neutral $\lambda_{max.}$/nm (log ε)	pK_a	Anion λ_{max} /nm (log ε)
H	H	H	H	470 (3.92)	9.0	574 (4.23)
Cl	H	H	CH_3	468 (3.84)	7.6	558 (4.19)
Cl	H	Cl	H	470 (3.82)	7.3	585 (4.22)
CH_3	H	Cl	H	480 (3.86)	8.7	620 (4.26)
H	CH_3	Cl	H	470 (3.83)	9.0	618 (4.23)

temperatures. This was also significant in reactions where solutions of the pure indophenol were available since hydrogen peroxide is also formed during the conversion of the aminoindophenol into the dihydroxyphenazine (3). Fortunately, it was found that *m*-aminophenols could act as scavengers for peroxide and that if *ca.* 4 molar proportions of *m*-aminophenol were present, it was possible to get quantitative yields of phenazine and good kinetic data, and a good spectrophotometric course with an isosbestic point was observed.

Accordingly kinetic reactions were performed using *p*-aminophenol, *m*-aminophenol, and potassium ferricyanide in the molar ratio 1 : 5 : 4 and adding the *m*-aminophenol last. In the case of 5-amino-2-methylphenol, which reacts too rapidly with ferricyanide, we studied only one derived indophenol which was available in the pure state.[2] *m*-Aminophenol was added to the solution as a peroxide scavenger.

When the visible spectrum of a solution of a 2-aminoindophenol is scanned at intervals, the absorption near 580 nm slowly disappears while a new band near 450 nm appears. On repeat scanning a sharp isosbestic point is observed at 480 nm. The rate of reaction can be calculated from the optical density *versus* time curve at either 450 or 580 nm. The rate was found to follow the first-order rate equation (2) where [P] is the phenazine

$$d[P]/dt = -d[In]/dt = k[In] \qquad (2)$$

concentration, [In] that of the indophenol, and *k* is the observed rate constant.

For each 2-aminoindophenol studied, the rate was determined at a number of different pH values in the range 7—12. The rate was found to be independent of pH at higher pH values and to decrease with decreasing pH at the lower end of the range. This would be consistent with the assumption that it is the 2-aminoindophenolate ion (2) which undergoes cyclization and that the neutral indophenol (1) does not. Table 2 gives typical rate data for the cyclization of 2-aminoindophenol. The observed rate constant was corrected for the spectrophotometrically determined yield of phenazine according to equation (3) where *k* is the observed and

$$k_1 = k\,(\%\ P/100)\,\alpha \qquad (3)$$

k_1 the true first order rate constant. The value of k_1 as a function of pH is given by equation (4) where k_a is the

$$k_1 = k_a\alpha \qquad (4)$$

specific first-order rate constant for the cyclization of the anion and α is the fraction of indophenol present as the anion at the pH to which k_1 pertains and can be calculated from the value of the pK_a given in Table 1. From Table 2 it can be seen that k_a is independent of pH which would be expected if the anion were indeed the reactive species. The cyclization can thus be represented as shown in the Scheme. The actual cyclizing species is probably the form (5) of the anion (2) and the rate-controlling step involves electrophilic attack by the imino-group on the carbon *ortho* to the azomethine bridge to give the dihydrophenazine (6) which undergoes rapid air oxidation to the phenazine (3).

TABLE 2

Rate data for the cyclization of 2-aminoindophenol (2) at 79 °C *

pH	10^4k/s^{-1}	Yield (%)	α	10^4k_a/s^{-1}
11.20	2.54	98	0.994	2.56
10.77	2.51	97	0.984	2.55
9.95	2.42	100	0.909	2.66
9.30	2.14	80	0.666	2.57
8.52	2.03	55	0.443	2.52

* Symbols as in equations (3) and (4).

In the case of 2-aminoindophenols having a 3′-substituent on the benzenoid ring, it was of interest to determine which of the possible 2,8-dihydroxyphenazines, the 7- or the 9-isomer, was formed. This was done by comparison with the products from the 2-aminoindophenols (2) having the same substituent in the 3- (giving the 9-substituted phenazine) and the 5-position (giving the 7-substituted phenazine). It was found that 2-amino-3′-methylindophenols gave 2,8-dihydroxy-9-methylphenazines (since they were spectrally identical to those formed from 2-amino-3-methylindophenols and different from those formed from the 5-methyl analogues). In contrast 2-amino-3′-chloroindophenols gave 2,8-dihydroxy-7-chlorophenazines (since they were different from those formed the 2-amino-3-chloroindophenols). This is in accord with the proposed mechanism since methyl would be expected to activate and chloro to deactivate the *ortho*-carbon towards electrophilic attack. All other indophenols give structurally unambiguous phenazines.

Table 3 gives values of k_a for the cyclization of a variety of 2-aminoindophenols at 79 °C. It can be seen that chloro-substitution of the quinonoid ring increases the rate of cyclization *ca.* 3-fold while similar substitution of the benzenoid ring decreases the rate by a factor of 2. On the other hand, methyl groups increase the rate *ca.* 3-fold when on the benzenoid ring but decrease it by a factor of 2 (3-methyl) or 5 (5-methyl) when on the quinonoid ring. Also, it should be noted that the substituent effects are cumulative. The fact that these

Table 3

Values of specific first-order rate constants (k_a) for formation of 2,8-dihydroxyphenazines from 2-aminoindophenols at 79 °C

Indophenol (2)				
3′-Subst.	2′-Subst.	4-Subst.	3-Subst.	$10^4k_1/s^{-1}$
H	H	H	H	2.57 ± 0.09
H	H	Cl	H	7.27 ± 0.09
H	H	H	CH_3	1.08
H	H	CH_3	H	(0.55 ± 0.04)
Cl	H	H	H	1.50 ± 0.07
Cl	H	Cl	H	4.47 ± 0.09
Cl	H	H	CH_3	0.54 ± 0.05
CH_3	H	H	H	7.00 ± 0.45
CH_3	H	Cl	H	15.3 ± 0.07
CH_3	H	H	CH_3	3.2 ± 0.11
CH_3	H	CH_3	H	(1.75 ± 0.09)
H	CH_3	Cl	H	17.2 ± 0.02

substituent effects are qualitatively similar to those observed[2,4] for oxidative coupling of quinone imines with phenols, further supports the proposed mechanism.

Spectral data for the dihydroxyphenazines (3) are given in Table 4. At high pH, the solutions are orange and the dye presumably exists as the dianion. On decreasing the pH, the solution becomes redder due to protonation of the 10-nitrogen atom. As pH decreases, a yellow species, presumably the neutral compound is formed. At pH < 3, the solution again becomes orange owing to the formation of the conjugate acid. These assignments are made with the aid of comparisons with the spectra of 2,8-dimethoxy- and 2,8-diamino-phenazines.[5] They are further supported by comparison with the spectra of the various ionic forms of 2,8-dihydroxy-3,10-dimethylphenazine which was obtained by oxidative coupling of *p*-aminophenol with 2-methyl 5-methylaminophenol, and cyclization of the resulting indophenol. By virtue of its quaternized nitrogen this phenazine cannot exist as the simple dianion. Instead, at pH > 7 it exists as the zwitterionic form having a spectrum and pK_a similar to that of the aza-protonated dianion of the unquaternized phenazines. At pH 4—6 2,8-dihydroxy-3,10-dimethylphenazine exists as a form having a spectrum and pK_a similar to that of the protonated monoanions of the simple dihydroxyphenazines and at pH < 3 the spectrum is similar to that of the protonated dihydroxyphenazines. pK_a Values for the various ionic species are also given in Table 4.

Table 4

Spectra and dissociation constants of 2,8-dihydroxyphenazines (3)

7-Subst.	9-Subst.	6-Subst.	1-Subst.	3-Subst.	Monocation λ/nm (log ε)	pK_a	Neutral λ/nm (log ε)	pK_a	Protonated dianion λ/nm (log ε)	pK_a	Dianion λ/nm (log ε)
H	H	H	H	H	427 (4.25)	3.0	395 (3.86)	6.5	494 (4.20)	8.8	443 (4.22)
H	H	H	Me	H	428 (4.11)	3.4	398 (3.93)	6.8	498 (4.15)	9.3	444 (4.18)
H	H	H	H	Me	430 (4.14)	3.2	393 (3.79)	6.9	501 (4.16)	9.2	441 (4.19)
Me	H	H	Me	H	432 (4.15)	3.1	395 (3.75)	7.0	505 (4.21)	9.3	445 (4.22)
H	H	H	Cl	H	430 (4.26)	2.5	401 (3.77)	5.9	500 (4.28)	8.6	446 (4.32)
H	H	H	H	Cl	428 (4.25)	3.2	396 (3.82)	6.5	495 (4.22)	8.6	442 (4.28)
Cl	H	H	Cl	H	430 (4.18)	2.2	403 (4.02)	5.2	504 (4.28)	7.9	448 (4.33)
Cl	H	H	H	Me	430 (3.95)	3.0	394 (3.70)	6.7	503 (4.02)	9.0	443 (4.09)
H	H	Me	Cl	H	425 (4.11)	2.6	399 (3.77)	5.9	495 (4.18)	8.7	443 (4.20)
H	Me	H	Cl	H	430 (4.00)	1.7	400 (3.74)	5.7	500 (4.13)	8.5	446 (4.20)
H	H	Me	H	H	424 (3.94)	3.9	394 (3.60)	6.9	492 (4.01)	9.1	440 (4.04)
H	H	H	H	Me (10-Me)	436 (4.26)	3.8	409 (4.06)	6.4	508 (4.38)		

While determining the pK_a values for the 2-aminoindophenols we noted that the compounds become unstable at low pH. The visible peak near 450 nm and the u.v. peak near 290 nm gradually disappeared and were replaced by a new absorption band near 275 nm. This was shown to be due to hydrolysis of the indophenol at the azomethine bridge to give the *p*-aminophenol and 2-amino-*p*-benzoquinone (4). The rate of disappearance of the indophenol followed the first-order rate law at constant pH and increased with decreasing pH. Over the pH range 2—5 the log k_h *versus* pH plot has a slope of -1. Below pH 2 the rate of increase in rate with decreasing pH decreases. This is not consistent with a mechanism involving the neutral indophenol (1) and the hydroxonium ion but rather the conjugate acid (7), a minority species, and water in the rate-controlling step. While it was not possible to determine the pK_a of the conjugate acid directly, we were able to estimate it by fitting the theoretical curve profile for log k' *versus* pH to the experimental points. In this way, the conjugate acid of 2-amino-5-methylindophenol was estimated to have pK_a *ca.* 1.1.

Rate data for the hydrolysis of 2-amino-5-methylindophenol are given in Table 5. The data fit equation (5)

$$k' = k_h\alpha \qquad (5)$$

where k' is the experimental first-order rate constant, k_h is the pseudo-first-order rate constant for the reaction of

Table 5

Rate data for the hydrolysis of 2-amino-5-methylindophenol at 30 °C

pH	$10^3k/s^{-1}$	Medium *	$[H^+]$	α	$10^3k/\alpha$
0.08	36.5	A	0.8133	0.909	40.1
0.27	34.6	A	0.427	0.863	40.1
0.52	30.8	A	0.302	0.799	38.6
0.68	26.7	A	0.209	0.715	37.3
1.05	11.7	B	0.0891	0.500	23.4
1.50	3.65	B	0.0699	0.285	12.8
2.61	0.58	B	0.0025	0.0307	18.9
3.00	0.214	C	10^{-3}	0.0124	17.2
4.0	0.033	C	10^{-4}	0.001 26	26.2
5.0	0.0038	C	10^{-5}	0.0001	38.0

* Medium: A, 1M-NaCl; B, 0.1M-Na_2SO_4; C, 0.1M-$NaOCOCH_3$.

the conjugate acid with water, and α is the fraction of the indophenol present as the conjugate acid at the pH to which k' pertains.

EXPERIMENTAL

Materials.—5-Methyl-2-aminoindophenol and 3′,5-dichloro-2-aminoindophenol were prepared as described previously.[6] Other indophenols were prepared in solution by adding to a buffer solution (3.0 ml), *para*-component (0.01 ml, 0.03M), potassium ferricyanide (0.02 ml, 0.06M), and *meta*-component (0.05 ml, 0.03M). In some cases, ferricyanide was omitted and the mixture was oxidized by air. Spectral and other data were recorded from these solutions as described previously.[3] Solutions could be stored for several hours at pH > 10 before noticeable decomposition occurred.

2,8-*Dihydroxyphenazine* (3).—2,8-Dihydroxyphenazine, m.p. >260°, was prepared by the HBr–acetic acid demethylation of 2,8-dimethoxyphenazine.[7] The brown solid was precipitated by ammonium hydroxide (Found: C, 68.0; H, 4.0; N, 13.1. Calc. for $C_{12}H_8N_2O$: C, 67.9; H, 3.77; N, 13.2%). This product gave spectral data identical to the cyclization product from the indophenol (1).

2-*Amino*-5-*methyl*-p-*benzoquinone* (4).—The product (4) of acid hydrolysis of 2-amino-5-methylindophenol was unstable in other than dilute solution. It was identical spectrally with the product from the reaction of 2-methyl-*p*-benzoquinone and ammonia, and from the acid-catalysed decomposition of 2-amino-5-methylindoaniline. Final identification was made by boiling the dye in dilute hydrochloric acid, and identifying the 2-hydroxybenzoquinone derivative produced by its characteristic spectrum.[8]

Kinetics.—Reaction rates were determined spectrophotometrically, using a Unicam SP 800A spectrophotometer, by repetitively scanning the visible spectrum of reacting solutions. Ionization constants were determined by standard spectrophotometric techniques and are accurate to ±0.1.

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