459. *The Mechanism of the Coupling of Diazonium Salts with Heterocyclic Compounds. Part II.* The Reaction of the Neutral Indole Molecule.*

By J. H. Binks and J. H. Ridd.

The reaction of diazonium ions with excess of indole has been studied in very dilute aqueous solution. The kinetics appear to be due to the superposition of two reactions, a normal azo-coupling reaction and an autocatalytic side-reaction that removes diazonium ions but does not form the azo-compound. Over the range pH4—6, the kinetics of the azo-coupling suggest that substitution occurs directly into the neutral indole molecule, and not by previous formation of the conjugate base. No deuterium isotope effect was observed.

INDOLE reacts readily with weak electrophilic reagents, such as iodine [1] or diazonium ions, in neutral or alkaline media. Monosubstitution occurs, apparently at the 3-position, and more complex products are often also produced. However, this reactivity may not be characteristic of the neutral indole molecule. Indole is a weak acid, and its reactions with electrophilic reagents may occur by the previous formation of the conjugate base; in this, it is sometimes compared with the feebly acidic phenols. The work now reported was carried out to resolve this uncertainty in the mechanism of substitution and to give a measure of the reactivity of the neutral indole molecule.

The colour reaction of indole with diazotised sulphanilic acid has long been known,[2] but few indole azo-compounds have been isolated pure. The reaction of indole with benzenediazonium chloride has been shown to give some 3-phenylazoindole,[3] and that with diazotised arsanilic acid gives an azo-compound that is probably substituted in the same position.[4] The only other well-defined azo-compound is that containing a *p*-bromophenylazo-group, prepared from indole and *p*-bromophenylazoxycarboxamide in alkaline solution.[5] Other azo-compounds have been prepared from substituted indoles.

A kinetic study has been made of the reaction of several diazotised amines with a tenfold excess of indole in aqueous solution at 25°. The solutions used were very dilute, and the reaction was followed by colorimetric estimation of the diazonium ions. At pH 6·68, the reaction with *p*-nitrobenzenediazonium ions obeyed the expected first-order equation, but this was not true of the reactions with the other diazonium ions. The plots of % of reaction against time (see Figure) show that the first-order form is modified by an apparent autocatalysis, and that this modifying term becomes more important as the reactivity of the diazonium ion is decreased. Experiments on the diazo-coupling with sulphanilic acid at different acidities showed that an increased degree of autocatalysis in the disappearance of diazonium ions coincided with a decreased yield of the azo-compound. The autocatalysis therefore arises from some further reaction of the diazonium ions either with the monoazo-compound or with some side product of the primary coupling reaction. In this pH region, the normal decomposition of the diazonium ions is itself partially autocatalysed, owing to coupling with the phenols formed; however this reaction is too slow to explain the autocatalysis observed.

The reaction with *p*-nitrobenzenediazonium ions was chosen for further study because of its simple kinetic form. A pure sample of the monoazo-compound was prepared, and this, by analogy with the derivative from diazotised aniline, is presumed to be 3-*p*-nitrophenylazoindole. The spectrum was studied over a range of acid and alkali concentrations,

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* Part I, *J.*, 1953, 3937.

[1] Pauly and Gundermann, *Ber.*, 1908, **41**, 3999.

[2] Ref. 1, footnote, p. 4004.

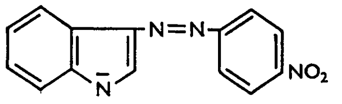
[3] Madelung and Wilhelm, *Ber.*, 1924, **57**, *B*, 234.

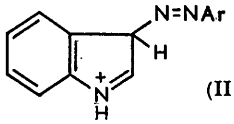
[4] Mingoia, *Gazzetta*, 1930, **60**, 134.

[5] Pieroni, *ibid.*, 1924, **54**, 157.

and the results were used to estimate the concentration of azo-compound formed in the kinetic experiments. The spectrum shows a marked change in alkaline solution, presumably owing to proton loss to form the 1-indolyl anion (I).

(I)

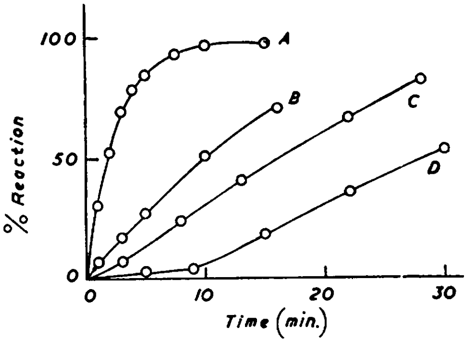




(II)

The yield of 3-*p*-nitrophenylazoindole as a function of pH is shown in Table 1; between pH 4 and 6 the yield is almost quantitative. These values were obtained by making the reaction mixture alkaline and comparing the spectrum with that of the 1-indolyl anion (I).

The kinetics of the reaction of indole with *p*-nitrobenzenediazonium ions were then studied in this pH range at 0°. Most of these kinetic runs were followed from the concentration of the azo-compound, but some were followed from the concentration of the diazonium ions; the two methods were in good agreement. A large excess of indole was used, and, as expected, the results fitted a first-order equation. This indicates that the reaction is of first order with respect to diazonium ions.



Reaction of diazonium ions with indole, as followed from the concentration of diazonium ion.

$[C_8H_7N] = 2{\cdot}5 \times 10^{-4}$. $[ArN_2^+] = 2{\cdot}5 \times 10^{-6}$.
pH = 6·68. Temp. = 25°.
A = p-*Nitroaniline.* *C* = *Sulphanilic acid.*
B = p-*Chloroaniline.* *D* = *Aniline.*

TABLE 1. *Yield of* p-*nitrophenylazoindole under conditions of kinetic experiments.*

$[C_8H_7N] = 5 \times 10^{-4}$M. $[ArN_2^+] = 25 \times 10^{-6}$M.

pH *	2·0	2·9	3·3	3·78	5·21	5·69	6·17	6·78	7·07	7·61
Yield, %	25·6	44·8	74·5	94·7	98·5	97·6	96·7	74·7	60·0	36·4

* All pH measurements were at 25°.

TABLE 2. *Determination of order with respect to indole.*

pH = 3·78. $[ArN_2^+] = 25 \times 10^{-6}$. Temp. = 0°.

$10^4[C_8H_7N]$	1·25	2·5 *	5·0 *	5·0	10·0
$10^4 k_1$ (sec.$^{-1}$)	3·04	6·3	11·1	11·3	26·1
k_2 (sec.$^{-1}$ mole^{-1} l.)	2·43	2·52	2·22	2·26	2·61

* These runs were followed from the concentration of diazonium-ion, the others from the concentration of azo-compound.

The first-order rate coefficients (k_1) for some of the kinetic runs are listed in Table 2, together with the second-order rate coefficients (k_2) obtained by dividing k_1 by the stoicheiometric concentration of indole in the solution. The results in Table 2 show that k_2 is effectively constant over an eight-fold increase in the indole concentration; the reaction is therefore of first order with respect to indole. The results in Table 3 show that this second-order rate coefficient varies only slightly over the pH range 3·78—6·17; over this range therefore, the kinetic equation does not also contain a pH-dependent term. The full kinetic equation is therefore rate = $k_2[C_8H_7N][ArN_2^+]$, where the concentration terms refer to the analytical or stoicheiometric concentrations of the reactants.

TABLE 3. *Variation of the second-order rate coefficient (in l. sec.$^{-1}$ mole^{-1}) with* pH.

$[C_8H_7N] = 5 \times 10^{-4}$. $[ArN_2]^+ = 25 \times 10^{-6}$. Temp. = 0°.

pH	3·78	4·55	4·87	5·21	5·69	6·17	6·68	6·78	7·61	8·60	9·20
k_2	2·26	2·24	2·18	2·20	2·08	2·04	3·10 *	3·16 *	3·90 *	5·20 *	4·50 *

All runs were followed from the concentration of azo-compound.
* These are approximate initial values; see text.

However, from the equilibrium constants for the diazo-equilibria,[6] and from the estimated basicity of indole,[7] it follows that, in this pH range, the actual concentrations of diazonium ions and indole molecules are both equal to their stoicheiometric values; the equation is therefore also thus when the concentration terms refer to the actual chemical species.

Much evidence suggests that diazonium ions are the effective electrophilic reagents in aqueous diazo-couplings.[8] The equation is clearly consistent with the direct reaction of diazonium ions with indole, and inconsistent with the prior formation of an equilibrium concentration of the indolyl anion. Hence, in these feebly acidic solutions, it appears that the observed reaction is due to the neutral indole molecule. Comparison with other kinetic results shows that, on a logarithmic scale, the reactivity of the indole molecule is about midway between that of the 1-naphthoxide ion and the neutral 1-naphthol molecule.[9]

More evidence on the reaction path is obtained by comparing the reactivity of indole and of 3-deuteroindole. Kinetic results for the reaction of *p*-nitrobenzenediazonium ions with indole and 3-deuteroindole are shown in Table 4; they indicate that the rate difference is slight and probably within the experimental error. This implies that the C–H and C–D bonds are not appreciably stretched in the rate-determining step; it therefore excludes the possibility that the ion (II) is formed in equilibrium concentration and then undergoes a slow rate-determining loss of a proton to a water molecule. The diazo-coupling of indole is therefore similar to that of the homocyclic compounds where, in the absence of steric hindrance, a slow attack of the diazonium ion is followed by a rapid loss of proton.[10]

TABLE 4. *Comparison of the azo-coupling of indole and 3-deuteroindole with* p-*nitrobenzenediazonium ions at* 0°.

$[C_8H_7N] = 5 \times 10^{-4}$. $[ArN_2^+] = 27{\cdot}7 \times 10^{-6}$. pH = 6·68.

	Time (min.)	1	2	3	4	5	10
Indole	10^6[azo-cpd.]	2·7	5·3	7·3	9·1	10·7	16·8
	10^4k_1 (sec.$^{-1}$).................	16·9	17·6	16·9	16·5	16·2	15·5
3-Deuteroindole	10^6[azo-cpd.]	3·1	5·3	7·2	8·9	10·6	16·4
	10^4k_1 (sec.$^{-1}$).................	19·6	17·6	16·6	16·1	16·1	15·0

Kinetic studies at higher values of pH are complicated by the partial conversion of the diazonium chloride into the diazo-hydroxide and the alkali diazoate. Since the diazonium ions are the only effective electrophilic reagent in diazo-coupling,[11] this shift in equilibrium concentration should reduce the rate of the coupling reaction. Also, with *p*-nitrobenzenediazonium ions, the yield of the azo-compound is decreased (Table 1). Nevertheless the initial rate of formation of the azo-compound is at first increased as the pH is raised above 6·2. This is shown by the second group of runs in Table 3. The second-order rate coefficients are the values of the mean rate of formation of the azo-compound during the first two minutes divided by the initial concentration of diazonium

[6] Grachev, *Zhur. obshchei Khim.*, 1947, **17**, 1834.
[7] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[8] Zollinger, *Chem. Reviews*, 1952, **51**, 347.
[9] *Idem, Helv. Chim. Acta*, 1953, **36**, 1070; see also J. H. Binks, Ph.D. Thesis, Univ. of London, 1956.
[10] Zollinger, *Experientia*, 1956, **12**, 165.
[11] Wittwer and Zollinger, *Helv. Chim. Acta*, 1954, **37**, 1954.

ion and by the concentration of indole. This method of calculation underestimates the initial rate coefficients, nevertheless the increase over the previous values is unmistakable. The experiments on 3-deuteroindole show that this rate increase cannot be due to assisted loss of proton in the transition state; it is therefore likely to arise from an alternative reaction path involving the conjugate base of indole.

EXPERIMENTAL

Samples of indole were purified immediately before use by sublimation *in vacuo*; the purified material had m. p. 52°. The amines were either recrystallised or distilled before use. The buffer reagents and the sodium nitrite were "AnalaR"; the latter was recrystallised twice from water and dried. Throughout the following account, the solvent was water, unless otherwise stated.

Kinetics.—When the kinetic runs were followed colorimetrically from the concentration of diazonium ion, the procedure was essentially as described in Part I, except that the concentration of hydrochloric acid during the diazotisation was 0·4N, and that 3-hydroxynaphthalene-2 : 7-disulphonic acid was used as the coupling reagent. The concentration of diazonium ions was determined before each kinetic run and this value was used in the calculations.

When the runs were followed from the concentration of azo-compound, a series of separate reaction mixtures was prepared from the same diazonium-ion solution. After an appropriate time, the reaction was stopped by adding a solution of potassium hydroxide in aqueous ethanol. The concentrations were adjusted so that the final concentration of potassium hydroxide was 0·1M in 50% ethanol by volume. The concentration of azo-compound was calculated by comparing the optical density of this solution with that of solutions of the pure azo-compound in the same medium.

Conventional buffering agents (phthalate, phosphate, or borate) were used in the kinetic runs, the combined concentration of the buffer acid and the conjugate base being 0·05—0·1M. The results suggest that the reaction rate is not very sensitive to the nature or concentration of the buffer solution.

Preparation of 3-*Deuteroindole.*—In the pH range 2·5—0·5, it has been shown that the 1- and the 3-hydrogen atom of indole can be exchanged with the deuterium of heavy water; at higher pH values only the 1-hydrogen atom can be exchanged.[12] 3-Deuteroindole was therefore prepared as below.

A suspension of indole (1 g.) in a mixture of heavy water (99·78%; 10 ml.) and deuterated hydrochloric acid (0·1N; 1 ml.) was stirred for 4 hr. at 60°. The indole was recovered by extraction with ether, and the process was repeated twice with fresh deuterating solutions. The deuterium atom at position 1 was then removed by treatment with potassium hydrogen phthalate solution (M/20; pH 4). After purification of the indole by sublimation, the analysis of the hydrogen produced by combustion and reduction corresponded to 93·1% exchange at a single position.

Preparation of the Azo-compounds.—*p*-Nitroaniline (3 g.) in dilute hydrochloric acid (325 ml.; 0·9N) was diazotised at 0° with sodium nitrite (2·5 g.) and added slowly to indole (2 g.) in dilute potassium hydroxide (5 g. of KOH in 800 ml. of water) containing crushed ice (200 g.). The red precipitate was dried (yield, 1·4 g.). Part of this was dissolved in benzene and chromatographed on alumina. After elution with benzene containing 5% of ethanol, the main orange band was separated and extracted with ethanol. Water was added to the ethanol solution, the minute red crystals were filtered off, the compound was again chromatographed, and the product crystallised from ethanol–water. The crystals had m. p. 195—197° (Found: C, 62·6; H, 3·7; N, 20·7. Calc for $C_{14}H_{10}N_4O_2$: C, 63·2; H, 3·8; N, 21·1%).

3-Phenylazoindole was prepared as above: it had m. p. 134—135° (Found: C, 76·1; H, 5·0; N, 18·6. Calc. for $C_{14}H_{11}N_3$: C, 75·9; H, 5·0; N, 19·1%). The mono-azo-compound from *p*-chloroaniline was similarly prepared except that the potassium hydroxide was omitted and the final crystallisation was from benzene. The product had m. p. 179—181° (Found: C, 65·8; H, 4·1; N, 17·1; Cl, 14·6. Calc. for $C_{14}H_{10}N_3Cl$: C, 65·7; H, 3·9; N, 16·4; Cl, 13·9%).

Spectra of the Azo-compounds.—In aqueous dioxan or aqueous ethanol, these compounds give a yellow solution. When the solutions are made alkaline, that of the *p*-nitrophenylazo-compound becomes purple, that of the *p*-chlorophenylazo-compound becomes pale orange

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[12] Koizumi and Titani, *Bull. Chem. Soc. Japan*, 1938, **13**, 307.

(but in a higher alkali concentration), and that of 3-phenylazoindole is unaffected. This order is as expected if the change is due to loss of proton.

These azo-compounds (as the neutral molecules) have one absorption maximum at about 280 mμ and a stronger maximum nearer the visible region. Ionisation increases the intensity of this second maximum and causes a marked shift to longer wavelengths. The spectra of 3-*p*-nitrophenylazoindole solutions were studied at different concentrations of hydroxide ion in 50% aqueous ethanol. The solutions obey Beer's law and have an isosbestic point at 482 mμ ($\varepsilon_\lambda = 1{\cdot}32 \times 10^4$); the ionisation appears to be almost complete when the stoicheiometric concentration of hydroxide ions is 0·05M. In contrast, 3-*p*-chlorophenylazoindole is not fully ionised when the concentration of hydroxide ion is 1·0M. Details of the main absorption maxima are summarised below.

Indole	Medium	$[OH^-]$ *	$\lambda_{max.}$, mμ	$10^{-4}\varepsilon$
3-*p*-Nitrophenylazo-	50% aq. ethanol †	—	440	2·11
,, ...	,,	0·05	550	3·56
3-*p*-Chlorophenylazo-	,,	—	372	2·66
,, ...	,,	1·0	446	3·24
3-Phenylazo-	5% dioxan–95% water †	—	368	1·61

* Stoicheiometric concentration. † By volume.

The authors thank Professors E. D. Hughes, F.R.S., and C. K. Ingold, F.R.S., for their interest and advice.

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[*Received, December* 28*th*, 1956.]