The Mechanism of Diazo-coupling to Indoles and the Effect of Steric Hindrance on the Rate-limiting Step

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The first syntheses of 4-methyl-2-t-butyl- and 2-methyl-4.6-di-t-butyl-indole are described. Rates of diazo-coupling at the 3-position of both these compounds together with those for 2-methyl- and 2-t-butyl-indole are reported for various *para*-substituted arenediazonium ions in mixed aqueous and some aprotic solvents at 25°. The kinetic behaviour of 2-methylindole is examined in detail and it is shown that 3-coupling may proceed through either the neutral compound or the 2-methylindolyl anion depending on the pH, with the anion being *ca.* 10^8-fold more reactive. For neutral 2-methylindole coupling, rates increase with increasing reactivity of the diazonium ion giving ρ 3.3 for the Hammett ($\rho\sigma^+$) plot. and for coupling with *p*-toluenediazonium ion $\Delta H^\ddagger$ = 38 kJ mol^{-1} and $\Delta S^\ddagger$ = 138 J K^{-1} mol^{-1}. Kinetic isotope effects for coupling to [3-^{2}H$_1$]- and [3-^{3}H$_1$]-2-methylindole and 3-deuteriated 2-t-butyl- and 4-methyl-2-t-butyl-indole are not apparent in aqueous dioxan. Coupling to 2-methyl-4.6-di-t-butylindole is also shown to proceed *via* both the neutral substrate and its conjugate base. but these reactions show significant primary hydrogen isotope effects (k^H/k^D *ca.* 7). The results are interpreted in terms of a classical A–S_E2 mechanism for both neutral indoles and indolyl anions in which direct electrophilic attack by the arene diazonium ion at the 3-position is normally rate limiting. The change in the rate limiting step observed for the A–S_E2 mechanism with 2-methyl-4.6-di-t-butylindole is attributed to steric hindrance acting only on proton expulsion in a very reactant-like transition state and not on attack of the electrophilic diazonium ion. There is no evidence for coupling to indole nitrogen and triazene intermediates are therefore not significant in any of these reactions.

ARENEDIAZONIUM ions are mildly electrophilic reagents capable of substituting activated aromatic compounds. The mechanism of these reactions is well established by the work of Zollinger,[1] who demonstrated an A–S_E2 mechanism (Scheme 1) for coupling to naphthols. With certain hindered hydroxy naphthalenesulphonic acids, the coupling reactions exhibited large primary deuterium isotope effects, which implied that proton transfer from the Wheland intermediate (step k_b) could be almost entirely rate limiting.[1a]

We have reported isotopic rate ratios for the hydrogen

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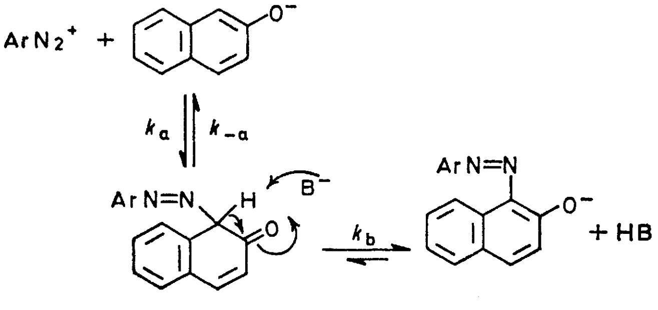
[1] H. Zollinger, *Helv. Chim. Acta* (*a*) 1955, **38**, 1597, 1617, 1623; (*b*) 1958, **41**, 2274. For a recent review see H. Zollinger, *Angew. Chem. Internat. Edn.*, 1972, **11**, 874.

[2] B. C. Challis and E. M. Millar, *J.C.S. Perkin II*, 1972 (*a*) 1116; (*b*) 1618, 1625.

exchange of indoles[2] and shown that their magnitude is largely independent of substrate reactivity and, *inter alia*, the symmetry of the transition state for proton transfer.[2b] Derivation of primary deuterium isotope effects for these reactions requires that assumptions be made about secondary isotope effects, so the data contain an undesirable element of uncertainty. Similar approximations are not required for diazo-coupling, so examination of these reactions may provide more accurate insight into the dependence of primary deuterium isotope effects on the transition state symmetry for proton transfer to and from aromatic substrates, as demonstrated, for example, by Zollinger and his colleagues[3] for hindered naphthols.



SCHEME 1 A–S_E2 Mechanism for diazo-coupling with 2-naptholate ion

Diazo-coupling to indoles has not been extensively investigated, but examination of aromatic nitrosation reveals a striking similarity between naphthols and indoles towards weakly electrophilic reagents.[4] Further, Binks and Ridd[5] have reported preliminary evidence for an A–S_E2 diazo-coupling mechanism for indole itself, although the kinetics were complex for most diazonium ions and the product yields low. These complexities may well arise from the incidence of 3,2-rearrangements,[6] which can be avoided with 2-alkylated indoles. Significantly, Binks and Ridd[5] found a deuterium isotope effect of unity, which suggests that rate-limiting proton transfer from the Wheland intermediate may be observed only with sterically hindered indoles, as for naphthols.[3,7] Their studies, however, did not clearly examine or establish reaction *via* the indolyl anion, although subsequent investigations of both indole hydrogen exchange reactions[8] and diazo-coupling to pyrroles[9] suggest this pathway could be important at high pH.

We have therefore examined the kinetics of diazo-coupling of several 2-methylindoles under a wide range of experimental conditions. These establish the reaction mechanism unequivocally and ascertain factors influencing the observation of substantial primary deuterium isotope effects.

EXPERIMENTAL

Substrates.—2-Methylindole (Koch-Light) and 2-t-butylindole (synthesised according to Jönsson[10]) were purified by vacuum sublimation to give m.p. 57—58° (lit.,[11] 59—60°) and 72—73° (lit.,[10] 73—74°), respectively.

4-*Methyl*-2-*t-butylindole* was prepared by treating 2,3-dimethylaniline with pivalolyl chloride and fusing the resultant anilide with Bu^{t}OK.[12] The yield was 60%, m.p. 86° (vacuum sublimed), $\nu_{max.}$ (Nujol–Kel-F) 3 390, 1 589, 1 540, 790, 771, and 698 cm^{-1}, δ (CCl_4) 1.33 (9 H, s), 2.52 (3 H, s), 6.27 (1 H, d, J 2.4 Hz), and 7.0 (3 H, m) (Found: C, 83.4; H, 9.2; N, 7.5. $C_{13}H_{17}N$ requires C, 83.4; H, 9.1; N, 7.5%).

2-*Methyl*-4,6-*di-t-butylindole*.—3,5-Di-t-butylbenzoic acid was prepared from 3,5-di-t-butyltoluene after Geuze *et al.*[13] and converted to 3,5-di-t-butylaniline by treatment with NaN_3 in H_2SO_4[14] (Found: C, 82.0; H, 11.1; N, 6.6. Calc. for $C_{14}H_{23}N$: C, 81.9; H, 11.3; N, 6.8%). 3,5-Di-t-butylaniline (80 g) in dry diglyme (250 ml) was heated under reflux with freshly prepared $NaNH_2$ (15 g) until evolution of NH_3 ceased, when 2-bromoacetaldehyde diethyl acetal[15] (70 g) was added dropwise. After heating under reflux for 1 h, the solvent was removed and excess of H_2O added. Ether extraction, followed by fractional vacuum distillation gave 2-(3,5-di-t-butylanilino)acetaldehyde diethyl acetal (30 g), b.p. 122—130° at 0.4 Torr, m/e 335 (M^+) and 232 (ArNH=CHMe). Treatment of this acetal with BF_3 in benzene at *ca.* 25° for 4 h,[15] followed by addition of excess of Et_3N, filtration, and removal of the solvent gave a thick oily residue. Chromatography on alumina (Merck Al) eluting with hexane–dichloromethane (10 : 90) gave 2-*methyl*-4,6-*di-t-butylindole* in 15% yield as the first eluted fraction, m.p. (from hexane) 172—173°, $\nu_{max.}$ (Nujol–hexachlorobutadiene) 3 370, 1 617, 1 548, 849, 784, and 755 cm^{-1}, δ (CCl_4) 1.35 (9 H, s), 1.45 (9H, s), 2.37 (3 H, s), 6.27 (1 H, m), 6.97 (2 H, s), and 7.4br (1 H, exchanges with D_2O), $\lambda_{max.}$ (50% w/w methanol) 223 (log ε 4.53) and 272 nm (3.95), m/e 243 (M^+) and 229 (M^+ − 15) (Found: C, 83.7; H, 10.3; N, 5.8. $C_{17}H_{26}N$ requires C, 83.8; H, 10.4; N, 5.8%).

Labelled Indoles.—Deuteriation was effected by dissolving the substrate (*ca.* 500 mg) in MeOD (10 ml) to which sodium metal (*ca.* 500 mg) had been previously added and allowing to stand overnight. Vacuum evaporation of the solvent followed by addition of H_2O precipitated

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[3] S. B. Hanna, C. Jermini, and H. Zollinger, *Tetrahedron Letters*, 1969, 4415.

[4] R. J. Higgins, Ph.D. Thesis, London, 1972; also compare B. C. Challis and R. J. Higgins, *J.C.S. Perkin II*, 1973, 1597; B. C. Challis and A. J. Lawson, *ibid.*, p. 918.

[5] J. H. Binks and J. H. Ridd, *J. Chem. Soc.*, 1957, 2398.

[6] G. Castnati, A. Dossena, and A. Pochini, *Tetrahedron Letters*. 1972, 5227; R. Iyer, A. H. Jackson, P. V. R. Shannon, and B. Naidoo, *J.C.S. Perkin II*, 1973, 872; V. G. Avramenko, V. D. Nazina, L. A. Polyakova, and O. Y. Okhlobystin, *Trudy Mosk. Khim. Teknol. Inst.*, 1970, 132.

[7] F. Snychers and H. Zollinger, *Tetrahedron Letters*, 1970, 2579; *Helv. Chim. Acta*, 1970, **53**, 1294.

[8] B. C. Challis and E. M. Millar, *J.C.S. Perkin II*, 1973, 1111.

[9] K. Mitsumura, Y. Hashida, S. Sekiguchi, and K. Matsui, *Bull. Chem. Soc. Japan*, 1973, **46**, 1770.

[10] A. Jönsson, *Svensk. kem. Tidskr.*, 1955, **67**, 188.

[11] N. B. Chapman, K. Clarke, and H. Hughes, *J. Chem. Soc.*, 1965, 1424.

[12] T. F. Tyson, *J. Amer. Chem. Soc.*, 1941, **63**, 2024; L. Marion and C. W. Oldfield, *Canad. J. Res.*, 1947, **25B**, 1.

[13] J. Geuze, C. Ruinard, J. Salterbrock, D. F. Verkade, and B. M. Wepster, *Rec. trav. chim.*, 1956, **75**, 301.

[14] T. W. Elder and R. P. Mariella, *Canad. J. Chem.*, 1963, **41**, 1653.

[15] M. Chastrette, *Ann. Chim.*, 1962, **7**, 643.

the product, which was filtered, dried, and purified by vacuum sublimation. Tritiation was effected similarly, using THO (1 ml; 20 mCi ml^{-1}) in methanol (10 ml).

Reagents.—Solutions of diazonium ions were prepared in two ways: by aqueous diazotisation of a standard solution of the corresponding amine [16] (reagent grade material purified by vacuum sublimation) or from the solid diazonium tetrafluoroborate (prepared according to Sakigara and Kikuchi,[17] and recrystallised repeatedly from acetone by the addition of hexane). Diazonium ion concentrations in solution were checked by their absorbance at *ca*. 280 nm, and the two methods gave close agreement.

Reagent grade dioxan (B.D.H.) was used without purification other than passage through a fresh Merck Al alumina column to remove peroxides. Deuterium oxide (N.m.r. Ltd; 99.7%) was used as supplied. Buffer solutions were prepared from AnalaR materials and their pH measured on a Radiometer 26 pH meter using a G202B glass electrode (calibrated with standard aqueous buffers).

TABLE 1

Physical data for 2,4,6-trisubstituted 3-arylazoindole hydrotetrafluoroborates

3-Aryl	2-Subst	4-Subst	6-Subst	*M*	$\nu_{max.}$/cm^{-1}	Chemical shift (δ)	$\lambda_{max.}$/nm (log ε)
p-MeC_6H_4	Me	H	H	249	3 220, 1 603, 1 550, 830, 760, 750	2.37 (3H, s), 2.77 (3H, s), 7.2—7.8 (7H, m), 8.42 (1H, m), 11.7br (2H)	282 (4.02) 377 (4.34)
p-MeC_6H_4	Bu^t	Me	H	305		1.75 (9H, s), 2.47 (3H, s), 2.83 (3H, s), 7.32—7.80 (7H, m)	
p-MeC_6H_4	Me	Bu^t	Bu^t	361	3 300, 1 630, 1 608, 1 062, 878, 809	1.35, 1.57 (18H, d), 2.34 (3H, s), 2.65 (3H, s), 7.18 (2H, s), 7.2—7.7 (2H, dd, *J* 8.2 Hz)	289 (4.14) 401 (4.19)
p-$MeOC_6H_4$	Me	Bu^t	Bu^t	377	3 270, 1 601, 1 060, 875, 840	1.34, 1.55 (18H, d), 2.61 (3H, s), 3.78 (3H, s), 6.98—7.72 (4H, dd, *J* 9 Hz), 7.14 (2H, s)	289 (4.16) 401 (4.22)

TABLE 2

Analytical data for 2,4,6-trisubstituted 3-arylazoindole hydrotetrafluoroborates

3-Aryl	2-Subst	4-Subst	6-Subst	Formula		C (%)	H (%)	N (%)
p-MeC_6H_4	Me	H	H	$C_{16}H_{16}N_3BF_4$	Found	57.1	4.95	12.25
					Required	57.0	4.8	12.45
p-MeC_6H_4	Bu^t	Me	H	$C_{20}H_{24}N_3BF_4$	Found	61.05	6.2	10.85
					Required	61.1	6.15	10.7
p-MeC_6H_4	Me	Bu^t	Bu^t	$C_{24}H_{32}N_3BF_4$	Found	64.45	7.2	9.4
					Required	64.15	7.15	9.35
p-$MeOC_6H_4$	Me	Bu^t	Bu^t	$C_{24}H_{32}N_3OBF_4$	Found	61.9	6.95	8.95
					Required	61.95	6.95	9.0
p-$NO_2C_6H_4$	Me	Bu^t	Bu^t	$C_{23}H_{29}N_4O_2BF_4$	Found	57.4	6.05	11.65
					Required	57.5	6.1	11.65

Products.—These were prepared by the addition of a solution of the indole (*ca*. 11 mmol) in acetone (10 ml) to the arenediazonium tetrafluoroborate (*ca*. 10 mmol) also in acetone (10 ml). After 20 min, hexane was added dropwise to precipitate the tetrafluoroborate of the azoindole. Absence of n.m.r. bands attributable to 3-H confirmed the site of the substitution in all cases. Confirmatory physical and analytical data are given in Tables 1 and 2 respectively.

Kinetics.—Rates of diazo-coupling at pH $\geqslant$3.5 were normally measured by u.v. assay of the reaction solution at the absorption maximum of the product ($\lambda_{max.}$ 377—401 nm). Coupling rates in dilute acid (pH <1) were followed similarly at the absorption maximum of the protonated 3-azoindole [$\lambda_{max.}$ 445 (for the 2-methyl derivative) and 525 nm (for the 2-methyl-4,6-di-t-butyl derivative)]. All measurements were taken with the reaction solution contained in a thermojacketted cell at 25 ± 0.1° using a Unicam SP 1800 spectrophotometer. Control experiments established the spontaneous decomposition rate of the diazonium ion under the coupling conditions and a small correction was applied where necessary. The final (' infinity ') absorption of the reaction solution was normally within 5% of its calculated value from the extinction coefficient of the purified product, although slow reactions showed lower values.

Several experiments employed the ' R-salt ' method [16] and gave good agreement with a direct spectrophotometric assay of the reaction solutions.

Simultaneous measurement of diazo-deprotonation and -detritiation rates required a modified technique. Here, at least a 10-fold excess of diazonium ion over indole was used and the reaction solutions were buffered to pH 7.3—7.8 to minimise both solvent-catalysed protodetritiation and homolytic decomposition of the diazonium ion [18] and products.[19] The kinetic runs were initiated by adding the [3-$^3H_1$]indole (*ca*. 1 mg in 0.5 ml dioxan) to the reaction solution (100 ml) in a volumetric flask. One portion was transferred to the thermojacketted spectrophotometer cell for continuous u.v. assay, whereas others (10 ml) were removed at timed intervals and their reaction quenched by shaking with xylene (15 ml). A portion of the xylene fraction (containing the indole substrate and product) was taken and air was passed through it for *ca*. 15 min to clear the solution and remove traces of THO. Radiometric assay was made with a Beckmann LS200 liquid scintillation counter, calibrated beforehand for the extensive quenching induced by the arylazoindole.

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[16] V. Machacek, O. Machackova, and V. Sterba, *Coll. Czech. Chem. Comm.*, 1971, **36**, 3186.

[17] M. Sukigara and S. Kikuchi, *Bull. Chem. Soc. Japan*, 1967, **40**, 1077.

[18] P. Burri, H. Loewenschuss, H. Zollinger, and G. K. Zwolinski, *Helv. Chim. Acta*, 1974, **57**, 395.

[19] (*a*) N. N. Bubnov, K. A. Bilevitch, L. A. Polyakova, and O. Y. Okhlobystin, *J.C.S. Chem. Comm.*, 1972, 1058; (*b*) S. McLean and G. I. Dmitrienko, *Canad. J. Chem.*, 1971, **49**, 3642.

Generally, diazodedeuteriation was examined in H_2O solvents and control experiments established that solvent-catalysed exchange of the substrate was negligible during the duration of the kinetic run. Where this condition was not met, D_2O was used instead of H_2O.

Calculation of Rate Coefficients.—All pseudo-first-order rate coefficients were evaluated by means of equations (1) or (2), where a and x refer to the final and transient

$$x = a - e^{-(k_0t+b)} \qquad (1)$$

$$x = a + e^{-(k_0t+b)} \qquad (2)$$

(at time = t) concentrations of the azoindole product in equation (1) or to the final and transient concentrations of the reactant in equation (2). Both expressions were treated by a non-linear least squares weighted regression method [20] to derive values k_0 and their standard errors. Data in Table 3 and 4 illustrate this analysis for the two principal methods of following the diazo-coupling rates. The accuracy of the rate constants was estimated to be better than ±6%.

TABLE 3

Simultaneous diazo-deprotonation and -detritiation of 2-methylindole in 40% (v/v) aqueous dioxan at pH 7.81 and 25°. Initial [p-$MeOC_6H_4N_2^+$] 5×10^{-3}M; initial (2-methylindole) *ca.* 4×10^{-5}M

	Diazodeprotonation		Diazodetritiation	
t/min	O.D. (380 nm)	O.D. (calc.)	C.p.m.	C.p.m. (calc.)
0	0.089	0.087	8 162	8 231
1	0.140	0.143		
2	0.195	0.195		
3	0.242	0.242	6 272	6 726
4	0.286	0.285		
6	0.361	0.361	4 815	4 774
8	0.425	0.425		
10	0.479	0.478	3 341	3 325
12	0.525	0.523		
14	0.562	0.561	2 309	2 319
18	0.621	0.619	1 643	1 621
22	0.660	0.660	1 113	1 137
28			679	674
∞	0.750	0.757 ± 0.004	40	40 ± 28

$k_0^H = 1.46 \times 10^{-3}\ s^{-1}$; $k_0^T = 1.52 \times 10^{-3}\ s^{-1}$.

Observed isotopic rate ratios $(k^H/k^D)_0$ were corrected for the isotopic purity of the deuteriated substrate (containing atom fraction of $[^2H_1] = n$) by means of equation (3).

$$k^H/k^D = (k^H/k^D)_0 n/[1 - (k^H/k^D)_0(1 - n)] \qquad (3)$$

The isotopic purity was determined by mass spectrometric assay.

RESULTS

2-*Methylindole.*—Coupling with toluene-p-diazonium chloride or tetrafluoroborate between pH 7 and −1 in 20% (v/v) dioxan at 25° was quantitative (>95%). At higher pH, however, the product yield dropped to *ca.* 50%, probably due to several adverse factors such as homolysis of the product,[19a] radical oxidation of 2-methylindole,[19b] and homolytic decomposition of the diazonium ion reagent.[18]

TABLE 4

Diazo-coupling of 2-methyl-4,6-di-t-butylindole in 40% (v/v) aqueous dioxan at pH 4 and 25°. Initial [p-$MeOC_6H_4N_2^+$] 4×10^{-5}M; [2-methyl-4,6-di-t-butylindole] 4×10^{-4}M

t/s	Reaction (%)	O.D. (401 nm)	O.D. (calc.)
0	0		0.005
50	6.4	0.060	0.064
100	12.5	0.121	0.120
150	18.1	0.179	0.172
200	23.4	0.222	0.221
300	32.9	0.308	0.309
400	41.3	0.385	0.386
500	48.7	0.451	0.454
600	55.1	0.511	0.513
800	65.5	0.610	0.610
1 000	73.7	0.686	0.685
1 250	81.2	0.758	0.754
1 750	90.2	0.838	0.838
2 000	93.1	0.861	0.864
∞		0.930	0.928 ± 0.004

$k_0 = 1.33 \times 10^{-3}\ s^{-1}$.

Zollinger [18] has suggested that the latter is exacerbated by electron-withdrawing aryl substituents, and, indeed, improved product yields (*ca.* 85%) were found even at pH 11 for p-methoxybenzenediazonium salts.

Kinetic Orders.—The A-S_E2 mechanism requires that the rate of coupling at constant pH follows equation (4)

$$\text{Rate} = k_2\,(\text{Indole})\,[ArN_2^+] \qquad (4)$$ *

which, of course, reduces to equation (5) when the substrate is in large excess. Except for the very slowest reactions ($t_{\frac{1}{2}} > 10^3$ s), the kinetic data followed equation (5) to

$$= k_0\,[ArN_2^+] \qquad (5)$$

greater than 90% reaction, as shown by the typical experiment cited in Table 3. For coupling to toluene-p-diazonium

TABLE 5

Diazodeprotonation of 2-methylindole in 20% (v/v) aqueous dioxan at pH̄ 3.5 ± 0.3 and 27.5°. Initial [p-$MeC_6H_4N_2^+$] 10^{-4}M

10^3[InH]/M	$10^3k_0/s^{-1}$	k_2/l s^{-1} mol^{-1}
5.5	11.5	2.09
4.0	8.16	2.08
3.0	6.45	2.14
2.0	4.20	2.10
1.4	3.03	2.16
0.5	0.97	1.95
0.25 [a]	0.52	2.08
0.1 [b]		1.9
1.0 [c]	1.58	1.58
0.1 [d]		1.55

[a] [p-$MeC_6H_4N_2^+Cl^-$] = 2.5×10^{-5}M. [b] Equimolar concentrations. [c] Followed by R-salt method, 0% dioxan. [d] Equimolar concentration, R-salt method, 0% dioxan.

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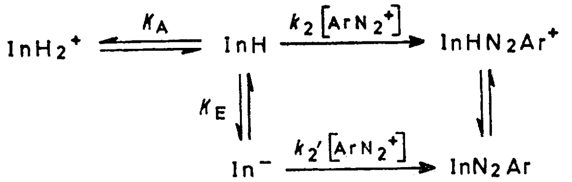
* Stoicheiometric reactant concentrations are denoted by round brackets and actual reactant concentrations by square brackets. Differences in the two are significant at certain pH because of prototropic equilibria. Thus [InH], [InH_2^+], and [In^-] denote actual concentrations of the neutral substrate, its conjugate acid, and base, respectively, whereas (Indole) represents the sum of all three. Rate coefficients dependent on stoicheiometric concentrations are denoted by a superscript bar.

[20] W. E. Deming, 'Statistical Adjustment of Data,' Wiley, New York, 1943; W. E. Wentworth, *J. Chem. Educ.*, 1965, **42**, 96, 162.

chloride in phthalate buffers (pH 3.5 ± 0.3), evidence in Table 5 shows that $\bar{k}_2$ is independent of (Indole) so the validity of equation (4) is established. Further, a consistent value for $\bar{k}_2$ is obtained from the reaction with equimolar reactant concentrations. Other data listed in Table 5 obtained by the ' R-salt ' method in purely aqueous phthalate buffers show that addition of 20% dioxan has only a small effect on the reaction rate.

Acidity Dependence.—Because 2-methylindole is both a weak base (pK_A -0.3) [21] and a weak acid (pK_E *ca.* 17),[22] $\bar{k}_2$ should be acidity dependent outside the pH range 1—7 with reaction proceeding *via* either the neutral or conjugate base species. The potential pathways to products allowing for the prototropic equilibria are summarised in Scheme 2.



SCHEME 2 Reaction pathways for diazo-coupling to indoles

The stoicheiometric coefficient $\bar{k}_2$ is related to the molecular coefficients for reaction *via* the neutral molecule (k_2) and the indolyl anion (k_2') by equation (6). Within the pH range 1—7, $\bar{k}_2 = k_2$ (because $K_A \gg [H_3O^+] \gg K_E$), but at other

$$\bar{k}_2 = \frac{k_2 + k_2'(K_E/[H_3O^+])}{[H_3O^+]/K_A + 1 + K_E/[H_3O^+]} \qquad (6)$$

pH values the molecular rate coefficients are conveniently evaluated from limiting equations.

Thus, at pH < 1, where reaction *via* the indolyl anion is negligible, equation (6) reduces to (7). The rate of coupling

$$[H_3O^+] = k_2K_A/\bar{k}_2 - K_A \qquad (7)$$

with *p*-toluenediazonium chloride was measured in HCl at constant ionic strength and the relevant plot of $1/\bar{k}_2$ *versus* $[H_3O^+]$ shown in Figure 1 gives k_2 *ca.* 2.1 l mol^{-1} s^{-1} and pK_A -0.14 at ionic strength of 2.0. Thus k_2 agrees well with that obtained in phthalate buffers (Table 5) which, in turn, suggests that base catalysis by phthalate ion is not significant. The pK_A is slightly different from that reported for pure H_2O (pK_A -0.30),[21] probably a consequence of deviation between the h_I acidity function [21] and $[H_3O^+]$ with high HCl concentrations. This deviation would also account for the non-linearity observed in Figure 1 at high [HCl].

In mildly alkaline solution (12 > pH > 9) reaction of the indolyl anion becomes important, despite its low concentration. Here, $K_E \ll [H_3O^+]$ and $K_A \gg [H_3O^+]$ so the kinetic expression approximates to equation (8).* Accurate

$$\bar{k}_2 = k_2 + k_2'K_E/[H_3O^+] \qquad (8)$$

measurement of coupling rates at this pH was possible only for *p*-methoxybenzenediazonium salts, and a plot of the relevant data (Figure 2) gives values of k_2 0.38 l mol^{-1} s^{-1} and $k_2'K_E$ 7 × 10^{10} s^{-1}. Since K_E *ca.* 10^{-17} l^{-1} mol for 2-methylindole in aqueous solution,[22] to a good approximation k_2' *ca.* 7 × 10^7 l mol^{-1} s^{-1}. The rate ratio for diazocoupling to the 2-methylindolyl anion relative to the neutral substrate k_2'/k_2 *ca.* 2 × 10^8.

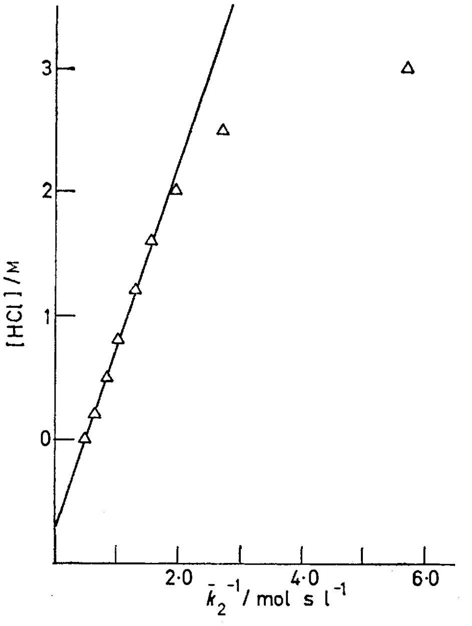


FIGURE 1 Acidity dependence of the rate of diazodeprotonation of 2-methylindole in dilute HCl at 25°

Activation Parameters.—The rate of coupling of *p*-toluenediazonium chloride in aqueous phthalate buffers (pH 3.0 ± 0.05) was also examined at several temperatures from 0 to 35.4° and these data are listed in Table 6. From a satisfactory linear plot of log $\bar{k}_2/T$ *versus* $1/T$ values of $\Delta H^\ddagger$ = 38 kJ mol^{-1} and $\Delta S^\ddagger$ = -138 J K^{-1} mol^{-1} were obtained.

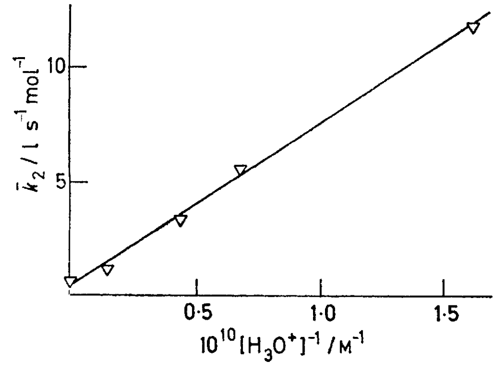


FIGURE 2 Rate of diazodeprotonation of 2-methylindole with *p*-methoxybenzenediazonium ion at high pH and 25°

Hydrogen Isotope Effects.—Isotopic rate ratios for

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* Equation (8) is valid only where conversion of the arenediazonium ion into the corresponding arenediazohydroxide is insignificant, as in the present studies.

[21] R. L. Hinman and J. Lang, *J. Amer. Chem. Soc.*, 1964, **86**, 3796.

[22] G. Yagil, *J. Phys. Chem.*, 1967, **71**, 1034, 1045; *Tetrahedron*, 1967, **23**, 2855.

coupling of the diazonium salt with the neutral 2-methylindole and its [3-$^2H_1$]isomer (k_2^H/k_2^D) and their corresponding anions ($k_2'^H/k_2'^D$) were both found to be 1.0 ± 0.2, showing the same behaviour as indole itself.[5] The corresponding tritium isotope effect (as shown in Table 3) was also unity. Together with the absence of significant base catalysis in phthalate buffers noted above, this implies that attack of the electrophilic diazonium ion, rather than proton loss from the Wheland intermediate, is fully rate limiting. This conclusion is borne out by the activation parameters given above which are significantly different from those found for isotopic hydrogen exchange ($\Delta H^\ddagger$ *ca.* 80 kJ mol^{-1}, $\Delta S^\ddagger$ -16 J K^{-1} mol^{-1}).[23]

TABLE 6

Temperature dependence of the rate of diazodeprotonation of 2-methylindole in H_2O at pH 3.0 ± 0.5. Initial [p-$MeC_6H_4N_2^+$] 10^{-4}M; (2-Methylindole) 10^{-3}M

T/°C	$\bar{k}_2$/l s^{-1} mol^{-1}
0	0.365
5	0.508
10	0.679
17.5	1.05
25	1.54
30	2.15
35.4	3.22

Hammett Relationship.—Apart from the p-methyl and p-methoxy-substituents noted above, coupling rates to the neutral 2-methylindole were also measured for other *para*-substituted benzenediazonium ions in 20% (v/v) aqueous dioxan at pH 4 ± 0.3. These data are summarised in Table 7 together with relevant values of σ^+ parameters. The corresponding Hammett ($\rho\sigma^+$) plot is linear giving ρ 3.3 (s 0.200; r 0.989).

TABLE 7

Coupling rates of 2-methylindole with *para*-substituted benzenediazonium ions in 20% (v/v) aqueous dioxan at 25°

Substituent	$\bar{k}_2$/l s^{-1} mol^{-1}	σ_p^+
MeO	0.37	−0.27
Me	1.8	−0.17
H	9.2	0.0
Cl	31	0.23
NO_2 [a]	2 700	0.78

[a] Extrapolated to 25° from 3° using the activation parameters given in text.

2-*t*-*Butyl*- *and* 4-*Methyl*-2-*t*-*butylindole.*—For these compounds measurements were limited to coupling rates of either toluene-p- or p-methoxybenzene-diazonium salts with the neutral indoles (see Table 8) principally to examine the effect of modest steric hindrance on their isotopic rate ratios. The results are summarised by three main observations. (*a*) 2-t-Butylindole couples at about half the rate of 2-methylindole, a difference entirely explicable in terms of the slightly reduced reactivity of the 2-t-butyl compound.[24] (*b*) The 4-methyl group has no significant effect on the coupling so steric and reactivity perturbations either cancel or both are negligible. (*c*) The deuterium isotope effect is negligible ($\bar{k}_2^H/\bar{k}_2^D$ 1.0 ± 0.2) so proton removal from the Wheland intermediate remains relatively rapid. All three findings clearly imply that steric requirements for substitution by the diazonium ion are small.

2-*Methyl*-4,6-*di*-*t*-*butylindole.*—Yields of azo-product here were normally better than 90% irrespective of the relative reactant concentrations up to pH *ca.* 9. Above this pH, excess of diazonium salt induced rapid autocatalytic decomposition of the product, but satisfactory yields and kinetics could be obtained up to pH 11 with an excess of the indole.

TABLE 8

Diazo-coupling of 2-t-butyl- and 4-methyl-2-t-butyl-indole in H_2O at pH 4.0 ± 0.6 and 25°. Initial [p-$MeC_6H_4N_2^+$] = 10^{-4}M. (Indole) = 10^{-3}M

Indole	Method	Dioxan (%)	$\bar{k}_2$/ l s^{-1} mol^{-1}
2-Bu^t	376 nm	20	0.750
2-Bu^t	376 nm	20	0.792
2-Bu^t	R-Salt	8	0.811
2-Bu^t	380 nm	20	0.188 [a]
2-Bu^t-3-$^2H_1$	376 nm	20	0.790
2-Bu^t-3-$^2H_1$	376 nm	20	0.823
4-Me-2-Bu^t	384 nm	40	0.737 [b]
4-Me-2-Bu^t	384 nm	40	0.677
4-Me-2-Bu^t-3-$^2H_1$	384 nm	40	0.651
4-Me-2-Bu^t-3-$^2H_1$	384 nm	40	0.683

[a] Using p-$MeOC_6H_4N_2^+$, all the other runs refer to p-$MeC_6H_4N_2^+$. [b] (Indole) = 2 × 10^{-3}M.

The kinetic form of the reaction with p-methoxybenzenediazonium salts was examined under pseudo-first-order conditions with an excess of either the indole or the diazonium salt. For coupling at pH 4 (phthalate buffers) in 40% (v/v) aqueous dioxan (to solubilise the substrate), it is clear from Table 9 that equation (4) is followed. The value of $\bar{k}_2$ (equivalent to k_2 under these conditions) is *ca.* 9-fold larger than that for 2-methylindole. This difference is accommodated (see earlier) by the increased basicity (reactivity) of the 2-methyl-4,6-di-t-butyl compound,[25] so any steric retardation by the 4-t-butyl substituent must be quite small. This matter is discussed further below.

TABLE 9

Kinetic orders for diazodeprotonation of 2-methyl-4,6-di-t-butylindole in 40% (v/v) aqueous dioxan at pH 4 and 25°

10^5 [Substrate]/M	10^5[p-$MeOC_6H_4N_2^+$]/ M	10^3k_0/ s^{-1}	$\bar{k}_2$/ l s^{-1} mol^{-1}
40	4	1.33	3.3
40	4	1.28	3.2
80	4	2.46	3.1
4	35	1.19	3.4
4	70	2.28	3.3
4	140	4.51	3.2
2	68	2.71	4.0 *
100	10	0.36	0.36 †

* At pH = 5.8 in presence of 1.0M-$MeCO_2Na$. † Rate for 2-methylindole.

The acidity dependence of the coupling rate of p-methoxybenzenediazonium salts was studied in a manner analogous to that for 2-methylindole. Thus in dilute aqueous H_2SO_4 containing only 4% (v/v) dioxan, the data are well fitted to equation (7) as shown by the reasonable linearity of Figure 3.

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[23] B. C. Challis and R. Iqbal, unpublished results.

[24] E. M. Millar, Ph.D. Thesis, London, 1968.

[25] B. C. Challis and H. S. Rzepa, to be published.

The agreement between pK_A values obtained from the slope (+0.6) and the intercept (+0.1) of Figure 3, however, is only modest, probably because protonation of 2-methyl-4,6-di-t-butylindole does not follow the usual h_I acidity function.[21] Nonetheless, these values clearly demonstrate that the di-t-butylated indole is more basic than 2-methylindole (pK_A −0.30 in H_2O).[21]

The rate of coupling at higher pH was examined in dilute tetraborate buffers, but the % dioxan had to be increased to 40% (v/v) for solubility reasons. Evidence summarised by Figure 4 demonstrates that both diazo-deprotonation and -dedeuteriation rates are well fitted by equation (8), so both the neutral indole and the indolyl anion are reactive under these conditions. Evaluation of the data leads to parameters (9) and (10), but neither one is directly comparable to those for 2-methylindole because of the change

$$\bar{k}_2^{H} = 3.1 + 5.9 \times 10^{-10}/[H_3O^+] \qquad (9)$$

$$\bar{k}_2^{D} = 1.5 + 3.6 \times 10^{-10}/[H_3O^+] \qquad (10)$$

in solvent. However, since the operational pH values (*i.e.* as measured with the glass electrode) for 20% (v/v) and 40% (v/v) aqueous dioxan are reasonably equivalent,[26] only differences in the K_E ionisation constants are significant.

The different slopes and intercepts of the two plots in Figure 4 imply that coupling to both 2-methyl-4,6-di-t-butylindole and its conjugate base is subject to a deuterium isotope effect. After correction for the isotopic purity of the [3-^{2}H] isomer (82%), the isotopic rate ratio for the neutral molecule reaction $k_2^{H}/k_2^{D} = 2.6 \pm 0.3$: for the anion reaction, $k_2'^{H}/k_2'^{D} = 2.0 \pm 0.2$ after correction as above and assuming that K_E is unaffected by isotopic substitution. The corresponding tritium isotope effect was measured for coupling of *p*-methoxybenzenediazonium ion to the neutral indole in phosphate buffers (pH 7.37) at 25° by following the rate of tritium loss and azo-product formation simultaneously (see Experimental section): these data gave $k_2^{H}/k_2^{T} = 5.1 \pm 0.3$.

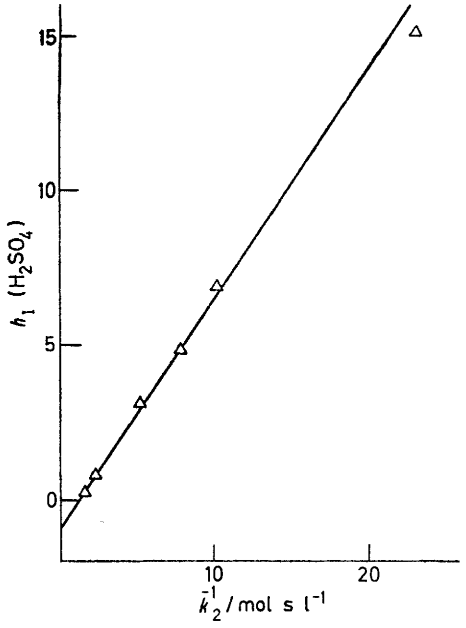

FIGURE 3 Acidity dependence for the diazodeprotonation of 2 methyl-4,6-di-t-butylindole in 4% (v/v) aqueous dioxan–H_2SO_4 at 25°

The observation of significant hydrogen isotope effects implies that base catalysis by the buffer components might be expected for coupling to 2-methyl-4,6-di-t-butylindole. Addition of 1.0M-$MeCO_2Na$ to the reaction mixture produced an insignificant increase in the reaction rate (see Table 9), so it seems that solvent water competes successfully with the buffer components in removing the proton from the Wheland intermediate.

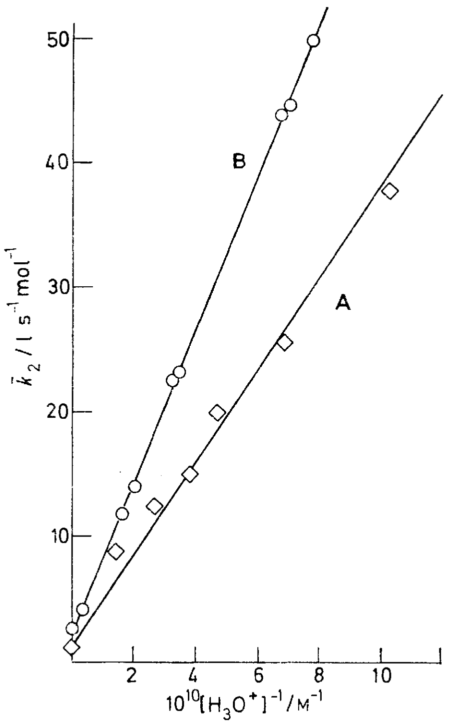

FIGURE 4 Acidity dependence for the diazocoupling of **A** [3-$^2H_1$]- and **B**, [3-$^1H_1$]-2-methyl-4,6-di-t-butylindole with, *p*-methoxybenzenediazonium ion in 40% (v/v) aqueous dioxan tetraborate buffers at 25°

DISCUSSION

All the experimental findings are consistent with a classical A–S_E2 mechanism (Scheme 3) for the diazocoupling reaction. Either the neutral indole or the indolyl anion is involved depending on the experimental conditions and application of steady state theory to each pathway gives equations (11) and (12) as familiar

$$k_2 = k_a/(1 + k_{-a}/k_b[B]) \qquad (11)$$

$$k_2' = k_a'/(1 + k_{-a}'/k_b'[B]) \qquad (12)$$

expressions relating the observed molecular rate coefficients to the invididual steps in Scheme 3. Reaction rates increase with the basicity (reactivity) of the substrate and are much faster for the indolyl anion: the rate ratio for coupling of *p*-methoxybenzenediazonium

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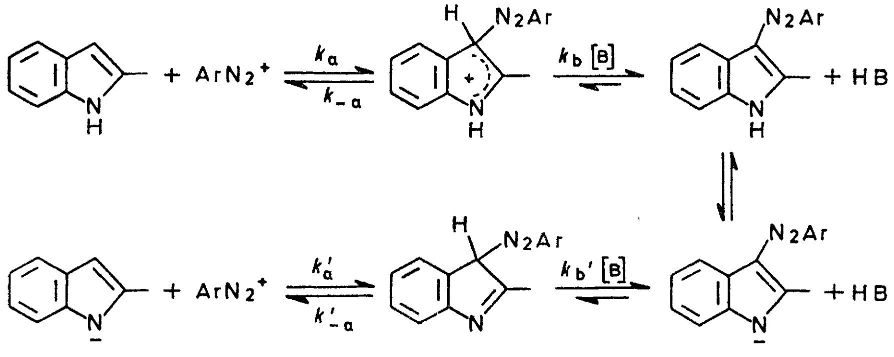
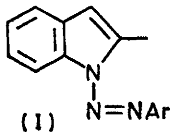
[26] L. G. Van Uitert and C. G. Haas, *J. Amer. Chem. Soc.*, 1953, **75**, 451.

ion to 2-methylindolyl anion relative to the neutral substrate is k_2'/k_2 *ca.* 2×10^8. This compares satisfactorily with equivalent ratios for diazo-coupling to 2-naphthol [27] and to pyrrole [9] (both *ca.* 10^8) and for hydrogen exchange at the 3-position of indoles (*ca.* 10^7).[28] Further, the magnitude of k_2' for reaction of the 2-methylindolyl anion with *p*-methoxybenzenediazonium salts is only *ca.* 100 fold less than that expected for a diffusion controlled reaction. Also reaction rates increase with increasing reactivity of the electrophilic diazonium ion and the value of ρ 3.3 for the Hammett ($\rho\sigma^+$) plot compares favourably with ρ 4.0 and 4.3—4.6 for diazo-coupling to aromatic amines [29] and pyrroles,[9] respectively. The activation parameters, particularly the highly negative $\Delta S^\ddagger$, are typical of other $A\text{-}S_E2$ reactions.[30]



SCHEME 3 $A\text{-}S_E2$ Mechanism for diazo-coupling to neutral indole and the indolyl anion

Because of the potential 1,3-ambident nucleophilic properties of the indole nucleus, there is a possibility, not eliminated by any of the findings discussed above, that 3-coupling proceeds by way of a triazene intermediate (I) or its conjugate acid. This question is of crucial importance, of course, to an interpretation of 3-H isotope effects, particularly if formation of the triazene proceeds at a comparable rate to that of the 3-azo-product. Triazene formation is well known [31] for primary and secondary aromatic amines and a reasonably comparable case to indoles is that of *N*-methylaniline, discussed by Beranek and his colleagues.[29a] Here, *N*-coupling is faster than *C*-coupling by a factor of 25, but is reversible at low pH to yield the thermodynamically stabler *C*-coupled aminoazobenzene.



(I)

For the neutral indoles, at least, the rate ratio for competitive *N*- and *C*-coupling should be much smaller, because the 3-position is inherently more basic than the *para*-position of *N*-methylaniline. *N*-Coupling is probably therefore insignificant and careful examination of the reaction products by both t.l.c. and u.v. gave no evidence of triazene formation. Further, slow *N*-coupling followed by a rapid thermal [1,3] sigmatropic rearrangement can be ruled out by the antarafacial pathway required from orbital symmetry considerations,[32] and a dissociative mechanism, comprising rapid *N*-coupling followed by slower *C*-coupling is equivalent (as far as isotope effects are concerned) to direct *C*-coupling and is unlikely because of the exact congruence between u.v. coupling and detritiation rates for [3-$^3H_1$]-2-methylindole. Also, the deuterium isotope effect for coupling to 2-methyl-4,6-di-t-butylindole confirms unequivocally that *N*-coupling is unimportant in this case: although the tritium isotope effect (k_2^H/k_2^T 5.1) could be explained by fast *N*-coupling followed by *ca.* five-fold slower rearrangement to the 3-azo-product, the deuterium isotope effect (k_2^H/k_2^D 2.6) cannot, because it is evaluated from equivalent experimental measurements and there is no possibility of a secondary 3-deuterium isotope effect of this magnitude on coupling to nitrogen.

The position is less clear cut with respect to *N*-coupling of the indolyl anions, but, significantly, no evidence of triazene formation was again found from careful u.v. and t.l.c. examination of the reaction products.

Evidently, with the exception of 2-methyl-4,6-di-t-butylindole, electrophilic attack by the diazonium ion (steps k_a and k_a' of Scheme 3) at the 3-position is normally rate limiting for azo-coupling to both neutral indoles and the indolyl anions in aqueous solvents. By implication, it seems that H_2O is a sufficiently effective base to ensure that both $k_{-b}/k_a[B] < 1$ and $k_{-b}'/k_a'[B] < 1$ so that equations (11) and (12) reduce to $k_2 = k_a$ and $k_2' = k_a'$, respectively. It follows that a change in the

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[27] K. Valter and V. Sterba, *Coll. Czech. Chem. Comm.*, 1972, **37**, 270.

[28] H. S. Rzepa, Ph.D. Thesis, London, 1974.

[29] (*a*) V. Beranek, H. Korinkova, P. Vetesnika, and M. Vecera, *Coll. Czech. Chem. Comm.*, 1972, **37**, 282; (*b*) V. Beranek and M. Vecera, *ibid.*, 1969, **34**, 2753.

[30] M. A. Matesich, *J. Org. Chem.*, 1967, **32**, 1258.

[31] I. T. Millar and H. D. Springall in N. V. Sidgewick, 'The Organic Chemistry of Nitrogen,' Clarendon Press, Oxford, 1966, 3rd edn., p. 602.

[32] R. B. Woodward and R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8**, 781.

rate-limiting step might be effected by coupling in aprotic solvents where the water concentration is significantly lower and reaction under these conditions was examined briefly. For 4-methyl-2-t-butylindole, small deuterium isotope effects (*ca.* 2) were found for coupling to toluene-*p*-diazonium salts in both nitrobenzene and nitromethane.

Findings for 2-methyl-4,6-di-t-butylindole show that a change of rate-limiting step, from attack of the electrophile to expulsion of the proton (step k_b of Scheme 3) is also effected by severe steric hindrance at the reactive site. Examination of the experimental isotopic rate ratios, however, clearly demonstrates that this change is incomplete with $k_{-b} \simeq k_a[\mathrm{B}]$. In particular, the Swain–Schaad[33] exponent (r) relating the tritium and deuterium isotope effects [equation (13)],

$$r = \log(k_2^{\mathrm{H}}/k_2^{\mathrm{T}})/\log(k_2^{\mathrm{H}}/k_2^{\mathrm{D}}) = 1.71 \qquad (13)$$

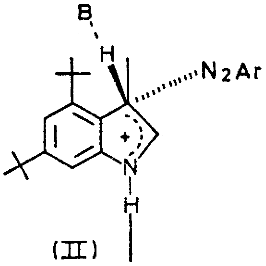
falls well outside the normally expected limits of $1.33 < r < 1.55$.[34] This is a direct consequence of k_2^{L} * being a composite rate coefficient as defined by equation (14). By assuming that the deuterium and

$$k_2^{\mathrm{L}} = k_a/(1 + k_{-a}/k_b^{\mathrm{L}}[\mathrm{B}]) \qquad (14)$$

tritium isotope effects for the k_b step fully comply with the Swain–Schaad relationship[33] (*i.e.* $\log k_b^{\mathrm{H}}/k_b^{\mathrm{T}} = 1.442\log k_b^{\mathrm{H}}/k_b^{\mathrm{D}}$) (calculations show that secondary isotope effects on k_a and k_{-a} are negligible), the observed isotopic rate coefficients (k_2^{L}) can be determined *via* equation (12) to give $k_b^{\mathrm{H}}/k_b^{\mathrm{D}} = 7$; $k_b^{\mathrm{H}}/k_b^{\mathrm{T}} = 18$; and $k_{-a}/k_b^{\mathrm{H}}[\mathrm{B}]$ *ca.* 0.31. These isotopic rate ratios are 'normal' in magnitude and very similar to those reported by Zollinger[1] for coupling to hydroxynaphthalenesulphonic acids. It should be emphasized however, that their accuracy is low because of the quality of the experimental data (±5%) and the approximation made, but they show how misleading isotopic rate ratios can be if proton transfer is not fully rate-limiting.

Our findings for sterically hindered indoles parallel those reported by Zollinger and his colleagues[1,7] for diazo-coupling to naphthols. They have firmly established in several investigations that substantial deuterium isotope effects, and base catalysis, are associated with sterically hindered substrates. From examination of the effects of *peri*-substituents on the 1-coupling rates of 2-naphthols, Snychers and Zollinger[7] have argued that the rate of electrophilic attack (step k_a of Scheme 1) is not subject to steric hindrance so the observation of a deuterium isotope effect, associated with an increase in the $k_{-a}/k_b[\mathrm{B}]$ ratio, must stem from a *decrease* in k_b rather than an increase in k_{-a} *i.e.* only expulsion of the proton is subject to steric interactions. The same argument applies satisfactorily for coupling to indoles. If $k_{-a}/k_b[\mathrm{B}]$ *ca.* 0.31 (see below) for reaction of *p*-methoxybenzenediazonium salts with neutral 2-methyl-4,6-di-t-butylindole, then k_a is *ca.* 12 fold larger than for the comparable reaction of 2-methylindole. This is consistent with their different basicities (reactivities), which implies that the k_a step is not subject to steric hindrance from the 4-t-butyl substituent. For coupling to the indolyl anions, the $k_2'K_{\mathrm{E}}$ product is closely similar for both the 2-methylindolyl and 2-methyl-4,6-di-t-butylindolyl reactants. Since the difference in K_{E} for each compound is probably <4,[28] the retardation induced by the 4-t-butyl substituent on k_a' is less than a factor of 5.

Following Snychers and Zollinger,[7] the deduction that steric hindrance operates only on proton expulsion from the Wheland intermediate, and not on attack by the electrophilic reagent, is indicative of an asymmetric σ-complex for the Wheland intermediate, and a correspondingly 'reactant-like' transition state (II) even for the proton-expulsion step. The incoming diazonium ion occupies a pseudo-axial position (towards the perpendicular to the indole ring) and is not greatly influenced by the periplanar t-butyl substituent: the leaving proton lies closer to the plane of the indole ring, and, because of the preferred linear reaction co-ordinate for proton transfer, the incoming base is subject to steric hindrance. Consequently, the rate of proton transfer is substantially decreased.



(II)

The introduction of further steric constraints into the substrate eventually affects the rate of diazonium ion attack. Thus coupling to 2,4,6-tri-t-butylindole is at least 10^3-fold less than expected from its basicity, and the eventual products largely consist of dealkylated azoindoles. It therefore seems that hindering the indole sufficiently to make proton expulsion completely rate limiting introduces undesirable side reactions.

Although diazo-coupling to indoles seems an unsuitable reaction for examining the kinetics of proton transfer, our results demonstrate that steric effects can be useful in determining the conformational properties of the transition state for proton transfer in these and related reactions.

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[4/2236 *Received*, 29*th October*, 1974]

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* The symbol L refers to isotopic hydrogen, *i.e.* H, D, or T.

[33] C. G. Swain, E. S. Stivers, J. F. Reuwar, and L. J. Schaad, *J. Amer. Chem. Soc.*, 1958, **80**, 5855.

[34] M. J. Stern and P. C. Vogel, *J. Amer. Chem. Soc.*, 1971, **93**, 4664.