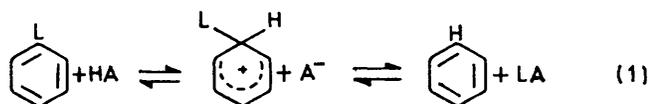


Heteroaromatic Hydrogen Exchange Reactions. Part IV.¹ Base-catalysed Protodetrithiation of 3-³H₁-Indoles in Aqueous Sodium Hydroxide

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Rates of protodetrithiation in aqueous NaOH at 25 °C are reported for eight indoles labelled at the 3-position. Both the catalytic effect of high [NaOH] and substituent effects on the rate are consistent with an S_E2 mechanism involving rate-limiting reaction between the indole anion and H₂O. The electrophilic nature of the reaction is demonstrated particularly by the large rate accelerations induced by 2-alkyl substituents, which can be attributed to extensive hyperconjugation in the neutral transition state. Values of the dissociation constant (K_B) for amino-hydrogen ionization obtained from the kinetic data are also reported. Various structure-reactivity relationships for the data are examined. The Brønsted relationship based on K_B values is unsatisfactory with an exponent in excess of the theoretical limit (β = 1.1). This arises from extensive charge delocalization accompanying attack at the 3-position, and a sensible Brønsted correlation can only be obtained with a parameter that directly measures the reactivity of this site. The application of H₋ acidity functions to kinetic data is also discussed.

ISOTOPIC hydrogen exchange of basic aromatic species usually proceeds *via* an A-S_E2 mechanism [equation (1)] involving the conjugate acid as an intermediate.² These reactions are convenient models for studying the fundamental phenomenon of proton transfer and have been closely examined for azulenes³ and aromatic ethers⁴ to this end. One undesirable limitation



imposed by hydrocarbon substrates arises from the difficulty of varying substrate reactivity without major structural alteration and, in this respect, heteroaromatic substrates appear to be more versatile.

We have reported on the incidence of both general

¹ Part III, B. C. Challis and F. A. Long, *J. Amer. Chem. Soc.*, 1972, in the press.

² V. Gold, 'Friedel-Crafts and Related Reactions,' ed., G. A. Olah, Interscience, New York, 1964, vol. 2, 1253.

³ F. A. Long and J. L. Longridge, *J. Amer. Chem. Soc.*, 1967, **89**, 1292, and references therein.

⁴ A. J. Kresge, Y. Chiang, and Y. Sato, *J. Amer. Chem. Soc.*, 1967, **89**, 4411, and references therein.

general acid- and general base-catalysed protodetrithiation reactions of 3-³H₁-2-methylindole,^{1,5} which are consistent with an S_E2 exchange mechanism and with the established acidic⁶ and basic properties⁷ of the compound. In this paper, the kinetics of the base-catalysed exchange process in aqueous sodium hydroxide solutions are examined in detail for several substituted indoles of differing reactivity.

EXPERIMENTAL

Substrates.—Indole and 2-methylindole were B.D.H. reagent grade chemicals; 5-bromo-, 5-cyano-, 5-methoxy-, 5-nitro-, and 6-nitro-indole were from the Aldrich Chemical Co.; 2-methyl-5-nitroindole was from the Regis Chemical Co.; 2-t-butylindole was synthesized by Jönsson's method⁸ and had m.p. 73 °C (lit.,⁸ 73–74 °C).

Tritiation Procedure.—Usually an acid-catalysed exchange between the substrate and tritiated water (THO)

⁵ Part II, B. C. Challis and F. A. Long, *J. Amer. Chem. Soc.*, 1972, in the press.

⁶ R. L. Hinman and J. Lang, *J. Amer. Chem. Soc.*, 1964, **86**, 3796.

⁷ G. Yagil, *J. Phys. Chem.*, 1967, **71**, 1034; *Tetrahedron*, 1967, **23**, 2855.

⁸ A. Jönsson, *Svensk. kem. Tidsskr.*, 1955, **67**, 188.

(supplied by The Radiochemical Centre, Amersham) was employed. The indole substrate (0.2–0.5 g) was dissolved in a homogeneous solution consisting of 1M-H₂SO₄ (2 ml), EtOH (5 ml), Et₂O (3 ml), and THO (2 ml, 8 mCi ml⁻¹). This mixture was stirred for *ca.* 30 min and then neutralized with solid Na₂CO₃. The labelled indole was extracted with diethyl ether (3 × 5 ml) and the ether removed at room temperature under vacuum after drying (CaSO₄). The residual solid was purified by repeated recrystallization or by vacuum sublimation to constant m.p.

The acid-catalysed procedure was unsuitable for 5-methoxyindole and indole itself because of extensive decomposition and polymerization. In these cases, labelling was carried out in alkaline solution. The substrate (0.5 g) together with NaOH (0.8 g) was dissolved in a mixture of EtOH (4 ml) and THO (5 ml, 4 mCi ml⁻¹) and the resultant homogeneous solution was stirred for 48 h. Then CO₂ gas was passed into the solution until the pH became 6 and the labelled indole was extracted with diethyl ether and purified as before. A sample of 3-³H₁-2-methylindole was also prepared by this procedure and its exchange rate in 0.1M-NaOH was identical to that prepared by the acid-catalysed method.

The site of isotopic substitution was ascertained by i.r. and n.m.r. examination of deuteriated analogues prepared under identical conditions apart from the substitution of 99.7% D₂O for THO. The details of these experiments are in Part V,⁹ where it is evident that both the acid- and base-catalysed labelling methods result in isotopic substitution at only the 1- and 3-positions and that tritium in the 1-position is replaced by hydrogen before the kinetic measurements merely by dissolving the labelled substrate in the aqueous reaction solution.

Reagents.—Carbonate-free sodium hydroxide solutions were prepared by dilution of a saturated solution of AnalaR sodium hydroxide with boiled-out distilled water. The molarity of these solutions was checked by titration against B.D.H. standardised HCl with Methyl Red as indicator.

Kinetics.—An almost saturated solution of tritiated indole was prepared first by stirring the solid compound in boiled-out distilled water for *ca.* 2 h. After filtration, a portion of this solution was added to the catalyst (NaOH solution with the addition of AnalaR NaCl in those cases where the ionic strength was maintained at a fixed value) contained in a volumetric flask immersed in a thermostatted tank at 25 ± 0.1 °C. For reactions at the highest NaOH concentrations, it was necessary to precool both catalyst and substrate solutions to combat heat of dilution effects. As soon as the temperature of the reaction solution had equilibrated to 25 °C, the volume was adjusted to the graduation mark by addition of distilled water. At suitable intervals, 10 ml aliquot portions were removed with a pipette and run into a 60 ml reagent bottle containing H₂O (5 ml) and sulphur-free xylene (15 ml). The contents were vigorously shaken for 1 min. The distribution coefficient of the indoles favours quantitative extraction from the aqueous phase by xylene. After the two phases had separated (*ca.* 1 h), 10 ml of the xylene layer was transferred to a counting vial containing 5 ml of scintillator solution {2,5-diphenyloxazole (4 g) and 1,4-bis-[2-(4-methyl-5-phenyloxazolyl)]benzene (0.1 g) in sulphur-free

* Throughout this paper, InH is the abbreviation for the neutral substrate and In⁻ for its conjugate base.

xylene (1 l)}. The radioactive assay was made with a Beckman LS100 liquid scintillation counter.

The decrease in radioactivity was a first-order process for at least five half-lives [equation (2)] and *k*₀ was evaluated from the experimental data by means of equation (3),

$$\text{Rate} = k_0[3\text{-}^3\text{H}_1\text{-InH}]^* \quad (2)$$

where c.p.m._{*t*₁}, c.p.m._{*t*_{*n*}} and c.p.m._∞ refer to counts per min of the first sample (at *t*₁ min), of subsequent samples (at *t*_{*n*} min), and after at least 10 half-lives, respectively. Checks

$$k_0 = \frac{2.303 \{ \log (\text{c.p.m.}_{t_1} - \text{c.p.m.}_{\infty}) - \log (\text{c.p.m.}_{t_n} - \text{c.p.m.}_{\infty}) \}}{t_1 - t_n} \quad (3)$$

established that no significant isotopic exchange took place during the sampling procedure and a typical kinetic experiment, representative of the accuracy of the data, is detailed in Table 1 for the exchange of 3-³H₁-5-nitroindole in 5.17M-NaOH.

RESULTS

Earlier investigation¹⁰ showed that the rate of protodetrutiation of 3-³H₁-2-methylindole varied linearly with base concentration up to 0.1M-NaOH. In more concentrated NaOH solutions, this simple dependence breaks down, particularly for compounds bearing electron-withdrawing groups on the aromatic ring. Variation of *k*₀ [equation (2)] with NaOH concentration is listed in Table 2

TABLE 1
Protodetrutiation of 3-³H₁-5-nitroindole in 5.17M-NaOH at 25 °C

Time (h)	Radioactive assay count min ⁻¹	Reaction (%)	10 ⁵ <i>k</i> ₀ /s ⁻¹
0.5	8238		
4.6	6857	16.5	1.25
10.5	5176	37.2	1.29
23.0	2854	65.5	1.32
28.5	2209	73.5	1.32
34.5	1682	79.9	1.31
47.5	923	89.1	1.31
∞	29		

for each compound studied and evidently *k*₀ increases linearly with NaOH concentration initially but then falls off to reach a limiting value. The trend is more easily seen from the plot of *k*₀ against [NaOH] for 3-³H₁-6-nitroindole in Figure 1.

The evidence in Part III¹ points to an S_B2 mechanism for the base-catalysed exchange of 3-³H₁-2-methylindole, involving a rate-limiting reaction between an acid catalyst (in this case H₂O) and the conjugate base of the substrate, formed in a relatively rapid pre-equilibrium step (Scheme).

Inspection of the variation of the second-order coefficient, *k*^T_{OH-} [equation (4)] derived from measurement at low [NaOH] where there is a first-order dependence on this quantity, with the acid dissociation constant of the sub-

$$\text{Rate} = k_{\text{OH}^-}^{\text{T}}[3\text{-}^3\text{H}_1\text{-InH}][\text{NaOH}] \quad (4)$$

strate (*K*_B) also eliminates ionization of the amino-hydrogen atom as the rate-limiting step. In this instance, the fastest rate would be associated with the most acidic

⁹ Part V, B. C. Challis and E. M. Millar, following paper.

¹⁰ B. C. Challis and F. A. Long, *J. Amer. Chem. Soc.*, 1963, **85**, 2524.

substrate, which is clearly not observed. Also the Brønsted plot of $\log k_{\text{OH}^-}^T$ against $\text{p}K_{\text{E}}$ (Figure 2) shows scatter well outside the experimental errors.

TABLE 2

First-order rate coefficients (k_0) for protodetritiation of 3- $^3\text{H}_1$ -indoles in aqueous NaOH at 25 °C

3- $^3\text{H}_1$ -5-Cyanoindole		3- $^3\text{H}_1$ -5-Bromoindole	
[NaOH]/M	$10^6 k_0/\text{s}^{-1}$	[NaOH]/M	$10^6 k_0/\text{s}^{-1}$
0.50	6.31	0.50	1.17
1.00	12.3	1.00	2.30
2.00	24.7	2.00	4.76
3.00	37.7	3.00	7.68
3.77	47.7	4.50	12.8
4.70	57.6	6.13	19.0
5.60	65.3	7.70	18.9
6.98	64.6	9.65	20.9
7.00	64.6		
8.40	60.5		
8.60	62.7		
10.03	57.6		

3- $^3\text{H}_1$ -6-Nitroindole		3- $^3\text{H}_1$ -5-Nitroindole	
[NaOH]/M	$10^6 k_0/\text{s}^{-1}$	[NaOH]/M	$10^6 k_0/\text{s}^{-1}$
0.10	1.36	0.20	1.57
0.15	1.96	0.30	2.24
0.20	2.62	0.50	3.62
0.25	3.27	1.00	6.72
0.40	4.88	2.00	11.1
0.80	8.65	2.60	13.1
1.00	10.2	3.20	14.1
1.20	11.5	4.16	14.5
1.40	12.7	5.17	13.1
2.00	15.2		
2.40	16.3		
2.80	16.8		
3.20	17.0		
3.60	16.4		
4.00	15.9		
4.08	15.7		

3- $^3\text{H}_1$ -2-Methyl-5-nitroindole		3- $^3\text{H}_1$ -Indole	
[NaOH]/M	$10^6 k_0/\text{s}^{-1}$	[NaOH]/M	$10^6 k_0/\text{s}^{-1}$
0.20	5.50	0.50	8.85
0.30	7.95	1.00	17.8
0.40	10.3	2.00	37.5
0.60	15.0	3.00	63.0
0.92	22.0	3.82	81.5
1.00	23.4	5.98	171
1.40	30.8	7.74	268
2.00	39.2	9.88	387
2.80	46.2	11.75	420
3.60	51.5	13.40	362
4.15	51.3		
5.11	47.5		

3- $^3\text{H}_1$ -2-Methylindole	
[NaOH]/M	$10^6 k_0/\text{s}^{-1}$
0.01	0.432
0.03	1.32
0.05	2.26
0.08	3.58
0.10	4.67
0.128	5.79

Observation of a limiting rate in concentrated NaOH is consistent, however, with the $S_{\text{E}2}$ mechanism and results from complete conversion of the substrate into the anion (I). The reaction rate can be expressed in terms of this anion concentration [equation (5)], where $k_{\text{bi}} = k_2 k_3 / (k_3 + k_{-2})$, and k_{bi} is therefore related to the experimental

$$\text{Rate} = k_{\text{bi}}[3\text{-}^3\text{H}_1\text{-In}^-][\text{H}_2\text{O}] \quad (5)$$

first-order coefficient (k_0) under non-steady state conditions

$$k_{\text{bi}} = \frac{k_0}{[\text{H}_2\text{O}]} \left(1 + \frac{[3\text{-}^3\text{H}_1\text{-InH}]}{[3\text{-}^3\text{H}_1\text{-In}^-]} \right) \quad (6)$$

by equation (6). Further simplification comes from expressing the substrate ratio ($[3\text{-}^3\text{H}_1\text{-InH}]/[3\text{-}^3\text{H}_1\text{-In}^-]$) in terms of the acid dissociation constant (K_{E}) for the

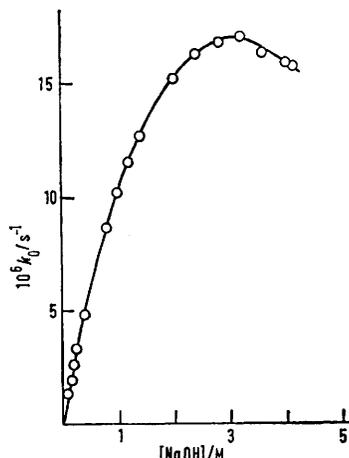


FIGURE 1 Plot of $10^6 k_0$ against $[\text{NaOH}]/\text{M}$ for the protodetritiation of 3- $^3\text{H}_1$ -6-nitroindole at 25 °C

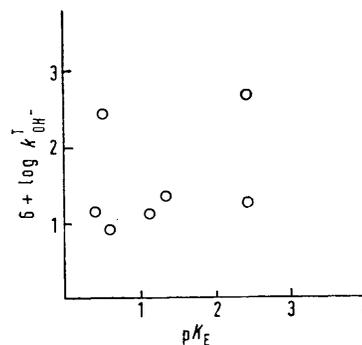
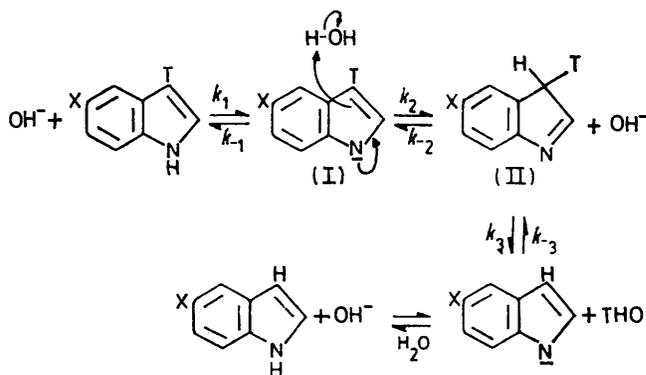


FIGURE 2 Plot of $6 + \log k_{\text{OH}^-}^T$ against $\text{p}K_{\text{E}}$ for the protodetritiation of 3- $^3\text{H}_1$ -indoles at 25 °C



$$K_{\text{E}} = \frac{k_1}{k_{-1}} = \frac{[\text{In}^-][\text{H}_2\text{O}]}{[\text{InH}][\text{OH}^-]}$$

SCHEME $S_{\text{E}2}$ Mechanism for the base-catalysed protodetritiation of 3- $^3\text{H}_1$ -indoles

rapid pre-equilibrium step [equation (7)]. By substituting for the substrate ratio, then taking reciprocals and arranging suitably, equation (8) is readily derived, which relates a

$$\frac{[3\text{-}^3\text{H}_1\text{-InH}]}{[3\text{-}^3\text{H}_1\text{-In}^-]} = \frac{[\text{H}_2\text{O}]}{K_E[\text{OH}^-]} \quad (7)$$

linear dependence between $[\text{H}_2\text{O}]/k_0$ and $[\text{H}_2\text{O}]/[\text{OH}^-]$. For measurements in concentrated alkali ($> 1\text{M-NaOH}$),

$$\frac{[\text{H}_2\text{O}]}{k_0} = \frac{1}{k_{\text{bi}}} + \frac{1}{K_E k_{\text{bi}}} \times \frac{[\text{H}_2\text{O}]}{[\text{OH}^-]} \quad (8)$$

it is advantageous to express the $[\text{OH}^-]$ in terms of the b_- acidity function described by Yagil and Anbar¹¹ and subsequently measured for NaOH solutions by Yagil⁷ [equation (9)]. Thus a plot of $[\text{H}_2\text{O}]/k_0$ against $[\text{H}_2\text{O}]/b_-$

$$\frac{[\text{H}_2\text{O}]}{k_0} = \frac{1}{k_{\text{bi}}} + \frac{1}{K_E k_{\text{bi}}} \cdot \frac{[\text{H}_2\text{O}]}{b_-} \quad (9)$$

should be linear with the intercept yielding values of k_{bi} , and K_E can be derived from the slope. The experimental

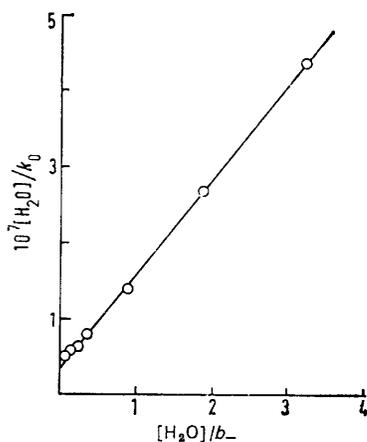


FIGURE 3 Reciprocal plot for the protodetrition of $3\text{-}^3\text{H}_1\text{-5-nitroindole}$ in aqueous NaOH at 25°C

data for all compounds other than $3\text{-}^3\text{H}_1\text{-2-methylindole}$ have been analysed in this way by use of the normalized 'free' water concentrations derived by Yagil and Anbar¹¹ for the $[\text{H}_2\text{O}]$ term. A typical plot for 5-nitroindole is given in Figure 3. Values of k_{bi} and K_E obtained are summarised in Table 3, together with K_E reported by Yagil⁷ from independent equilibrium measurements in aqueous NaOH solutions.

For 2-methyl- and 2-*t*-butyl- $3\text{-}^3\text{H}_1\text{-indole}$, the acquisition of accurate kinetic data in concentrated NaOH solutions is difficult because of their high reactivity and it is unsatisfactory to evaluate k_{bi} from a reciprocal plot. These coefficients can be obtained, however, from equation (10)

$$k_{\text{bi}} = k_{\text{OH}^-}^{\text{T}}/K_E \quad (10)$$

which is applicable to the $S_{\text{E}2}$ mechanism when the anion (I) is at low, steady-state concentration (*i.e.*, at low $[\text{NaOH}]$). As the acid dissociation constant (K_E) for neither of the 2-alkylindoles has been measured directly, we have evaluated k_{bi} from the K_E for indole itself (*i.e.*, $K_E = 2.45$). This seems a reasonable approximation since the data for 5-nitro-compounds (Table 2) show that the 2-methyl substituent has a negligible effect on the magnitude of K_E .

DISCUSSION

Agreement between K_E values derived from the rate of protodetrition and from independent equilibrium studies is generally quite good (Table 3). This vindicates the treatment of the kinetic data and, in turn, strongly supports the incidence of an $S_{\text{E}2}$ exchange mechanism. Substituents at both the 5- and 6-positions may conjugate directly with electrons on the heterocyclic nitrogen and, accordingly, electron-withdrawing groups (such as NO_2) will raise the acidity of the substrate by stabilizing the anion (I). By contrast, the same groups should decrease the rate of isotopic hydrogen exchange at the 3-position as this involves electrophilic attack by H_2O on the anion (I). Both consequences are clearly

TABLE 3

Second-order rate coefficients, k_{bi} , for protodetrition in NaOH at 25°C and acid dissociation constants ($\text{p}K_E$ and $\text{p}K_{\text{BH}^+}$) for substituted $3\text{-}^3\text{H}_1\text{-indoles}$

Substituent	$\text{p}K_E^a$	$-(\text{p}K_{\text{BH}^+})$	$10^5 k_{\text{bi}}/1 \text{ mol}^{-1} \text{ s}^{-1}$	$10^5 k_{\text{OH}^-}^{\text{T}}/1 \text{ mol}^{-1} \text{ s}^{-1}$
2-Me	2.45 (2.97) ^b	3.5 ^d	506	1.78
5- NO_2	2.45	0.3 ^d	10,130 ^f	45.4
5- NO_2	0.59 (0.69) ^b	7.4 ^d	3.13	0.785
5-CN	1.15 (1.21) ^b	6.0 ^e	13.9	1.25
5-Br	1.37 (2.32) ^b	4.3 ^e	46.7	2.34
6- NO_2	0.40 (0.59) ^c	6.9 ^e	3.57	1.32
2-Me, 5- NO_2	0.55	3.6 ^d	102	27.0

^a Values in parentheses are from equilibrium measurements.

^b Ref. 7. ^c B. C. Challis, unpublished results. ^d Ref. 6.

^e E. M. Millar, Ph.D. Thesis, St. Andrews, 1968. ^f Computed directly from $k_{\text{OH}^-}^{\text{T}}$ (see text).

observed, with a 5- NO_2 substituent, for example, raising the substrate acidity by a factor of *ca.* 260 and decreasing k_{bi} over 100 fold.

One other consequence of the $S_{\text{E}2}$ mechanism is that the exchange kinetics correspond to a general-base catalysed proton abstraction from H_2O [equation (5)], with the indole anion acting as catalyst. Thus the k_{bi} coefficient should correlate with substrate reactivity by way of the Brønsted relationship. An obvious choice to represent substrate reactivity in this instance is the acid dissociation constant K_E . In practice, however, this proves highly unsatisfactory. Figure 4 shows that the plot of $\log k_{\text{bi}}$ against $\text{p}K_E$ is poorly linear, with the data for 2-alkylindoles lying well above the line drawn through those for other substrates. Of even greater significance is that the minimum slope ($\beta = 1.1$) exceeds the theoretical limit for a Brønsted plot ($0 < \beta < 1$).

This poor correlation does not invalidate the $S_{\text{E}2}$ mechanism for exchange. We have shown¹ that a reasonable Brønsted relationship with $\alpha = 0.86$ pertains to the base-catalysed exchange rates of $3\text{-}^3\text{H}_1\text{-2-methylindole}$ when the catalyst strength is varied. Also excessive Brønsted exponents have been reported by Bordwell and his colleagues¹² for proton abstraction

¹¹ G. Yagil and M. Anbar, *J. Amer. Chem. Soc.*, 1963, **85**, 2376.

¹² F. G. Bordwell, W. J. Boyle, and K. C. Lee, *J. Amer. Chem. Soc.*, 1970, **92**, 5926.

from nitroalkanes where, too, the substrate, rather than catalyst, reactivity is varied and the phenomenon has been tentatively associated either with extensive structural or solvent reorganization accompanying

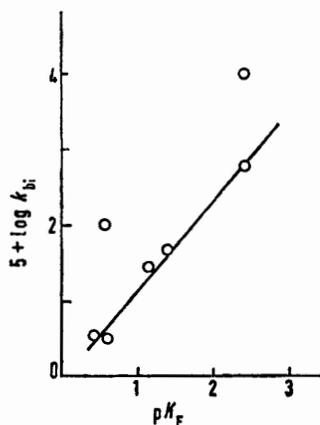


FIGURE 4 Brønsted plot based on pK_E for the protodetritiation of 3- 3H_1 -indoles at 25 °C. The slope of the line is 1.1

conjugate base formation from the carbon acid¹³ or with additional interactions of the catalyst and substituent in the transition state.¹⁴ Because of the remote disposition of the 5-substituent from the reactive site, it is the structural reorganization that must undermine the Brønsted plot for hydrogen exchange of indoles in Figure 4. Given that $k_{bi} = k_2/(1 - k_2/k_3)$ and if it is assumed, as in the acid-catalysed exchange,¹⁵ that the isotopic rate ratio (k_2/k_3) is relatively insensitive to substrate basicity, the structural variations of k_{bi} mainly reflect changes in the k_2 coefficient. Thus the value of $\beta = 1.1$ implies that protonation at the 3-position, which ultimately leads to hydrogen exchange and clearly requires extensive delocalization of the negative charge from nitrogen, is more sensitive to structural changes than is ionization of the amino-hydrogen atom. The situation is similar to that for the ionization of nitroalkanes where the oxygen atom (and not the reactive α -carbon atom) bears much of the negative charge of the conjugate base.

The other major factor in the breakdown of the Brønsted relationship based on pK_E values, the unusually large accelerative effect of 2-alkyl substituents, is not directly related to the structural reorganization discussed above. Methylation of the 2-position increases the exchange rate by a factor of 30 for both the 5-nitro- and unsubstituted compounds, without any comparable effect on the acid dissociation constant (K_E). This difference is clearly inconsistent with any polar interaction of the methyl substituent, but it can be explained in terms of hyperconjugative electron release. Strong support for this interpretation comes from the lesser effect of the 2-*t*-butyl group: in 0.1M-NaOH, $k_0 = 1.66 \times 10^{-5} \text{ s}^{-1}$, which corresponds to an increase of

¹³ R. A. Marcus, *J. Amer. Chem. Soc.*, 1969, **91**, 7224.

¹⁴ A. J. Kresge, *J. Amer. Chem. Soc.*, 1970, **92**, 3210.

¹⁵ Part VI, B. C. Challis and E. M. Millar, unpublished results.

about 9.3 compared to the exchange rate for 3- 3H_1 -indole itself. Extensive hyperconjugation is unexpected for a pathway involving the indole anion and the neutral 3H-indole intermediate (II) since development of positive charge in the transition state should be low, but it is consistent with the electrophilic character of the exchange process, whose sensitivity to charge stabilization must be considerably enhanced by the low reactivity of the attacking H_2O . Thus the poor correlation for 2-alkylindoles in Figure 4 arises from the opposite electronic requirements of the anion (I) and the transition state. As expected, the 2-methyl substituent enhances the acid-catalysed exchange rate involving the H_3O^+ catalyst by a factor of 70,¹⁵ which is low compared with that for substituted benzenes.¹⁶

The influence of both perturbations discussed above can be counteracted by correlating exchange rates with an alternative parameter for substrate reactivity. Neutral indoles are relatively weak bases, but dissociation constants for the conjugate acid (K_{BH^+}) are known^{6,15} (Table 3). These refer, of course, to proton removal from the 3-position [equation (11)], but they should also reflect the relative basicity of this site for the anion (I). The resultant plot of $\log k_{bi}$ against pK_{BH^+} (Figure 5) is reasonably linear and, in particular, the

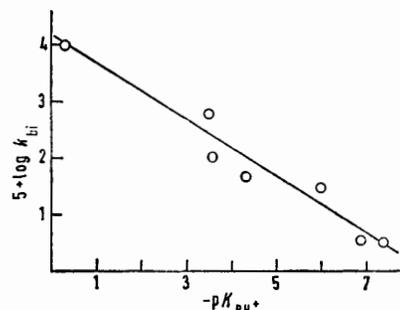
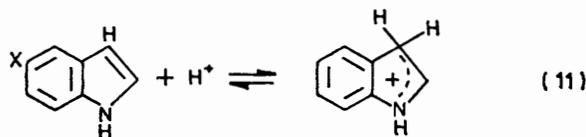


FIGURE 5 Brønsted plot based on pK_{BH^+} for the protodetritiation of 3- 3H_1 -indoles at 25 °C. The slope of the line is -0.5

high reactivity of the 2-alkylated substrates is well accommodated. The slope ($\alpha = 0.50$) lies within the theoretical limits, but its magnitude is not related to the degree of proton transfer in the transition state. In fact, other results for 3- 3H_1 -2-methylindole suggest that the transition state for hydrogen exchange is very unsymmetrical.¹



Acidity Function Correlations.—The application of kinetic H_- acidity function correlations to the resolution of mechanistic problems has not been widely examined, although the options have been discussed by Anbar and

¹⁶ R. O. C. Norman and R. Taylor, 'Electrophilic Substitution in Benzenoid Compounds,' Elsevier, London, 1965, p. 207.

his colleagues.¹⁷ For a bimolecular interaction of water with a conjugate base species they conclude that the rate may be proportional to either $[\text{OH}^-]$ (as predicted by the Zucker-Hammett criterion for an A_2 reaction)

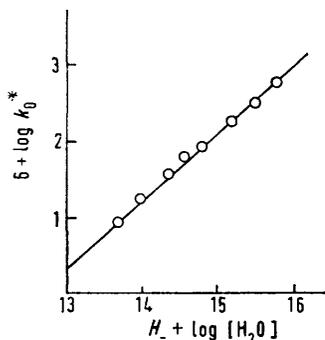


FIGURE 6 Plot of $6 + \log k_0^*$ against $H_+ + \log [\text{H}_2\text{O}]$ for the protodetrition of $3\text{-}^3\text{H}_1$ -indole in aqueous NaOH at 25 °C. The slope of the line is 0.95

or the product $b_- \cdot [\text{H}_2\text{O}]$. The present results allow a distinction between these alternatives. The analysis of the kinetic data discussed earlier which led to the

$$k_0^* = k_0 (1 + [\text{In}^-]/[\text{InH}])$$

¹⁷ M. Anbar, M. Bobtelsky, D. Samuel, B. Silver, and G. Yagil, *J. Amer. Chem. Soc.*, 1963, **85**, 2380.

derivation of equation (9) implies that isotopic hydrogen exchange conforms with the second option. The credibility of the correlation is manifest in the plot of $\log k_0^*$ against $H_+ + \log [\text{H}_2\text{O}]$ for the protodetrition of $3\text{-}^3\text{H}_1$ -indole in Figure 6. This is linear with slope 0.95, which implies that f^\ddagger is very similar to f_{In^-} . Two explanations for their similarity are apparent. One is that very little proton transfer from the water catalyst occurs in the transition state, but this is inconsistent with the large Brønsted α for general-acid catalysed protodetrition of $3\text{-}^3\text{H}_1$ -2-methylindole anion and with the instability of the 3H-indole tautomer, an intermediate on the reaction path.¹ The other, more likely, explanation is that solvation of both the anionic reactant and the transition state is not extensive. This suggests that kinetic acidity function correlations of anionic reactants will not be as diverse as those found for A_2 reactions in acidic media, where conjugate acid species are important reaction intermediates.¹⁸

We thank the S.R.C. for an equipment grant and for a maintenance grant (to E. M. M.).

[1/2418 Received, 16th December, 1971]

¹⁸ C. H. Rochester, 'Progress in Reaction Kinetics, eds., K. R. Jennings and R. B. Cundall, Pergamon, London, 1971, vol. 6, 143.