# Heteroaromatic Hydrogen Exchange Reactions. Part VI.[1] Isotope Effect for the Acid-catalysed Exchange of Some 3-$^2H_1$- and 3-$^3H_1$-Indoles

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Rates of deuterium and tritium displacement at 25 °C from the 3-position of indole, 5-methoxyindole, and 5-cyanoindole are reported for various aqueous acetic acid buffer solutions, together with data for indole in aqueous pyridine buffers and for indole and 5-cyanoindole in dilute HCl. Deuterium is displaced more readily than tritium throughout, and the incidence of general acid catalysis suggests a common $A$–$S_E2$ exchange mechanism. Isotopic rate ratios computed from the experimental data for this pathway are substantial ($k_H/k_D$ = 4·5—6·3) and show little systematic variation with the reactivity of either the substrate or the acid catalyst. Comparison with earlier data shows that the indole substrates are not exceptional in this respect and the size of the kinetic isotope effect appears to be an insensitive, if not unsatisfactory, index of transition state symmetry for aromatic hydrogen exchange reactions. Brønsted exponents for $H_3O^+$- and HOAc- catalysed exchange of these indoles are $\beta$ = 0·67 and $\beta$ = 0·75, respectively. Both are significantly larger than the Brønsted exponent obtained by the variation of the acid catalyst for exchange of 2-methylindole.

THE relevance of transition-state configuration to the magnitude of kinetic hydrogen isotope effects and to other kinetic parameters for proton transfer has been widely discussed in the literature.[2] Until recently, there has been fairly general concurrence with Westheimer's [3] early suggestion, based on much-simplified model calculations, that maximum primary isotope effects should come from symmetrical displacement of the proton along the reaction co-ordinate and much experimental evidence has been interpreted in this way.[4] Bell and Goodall,[4a] for example, have shown that $k_H/k_D$ ratios for proton abstraction from several aliphatic pseudo-acids pass through a maximum when the base strengths of the acid and catalyst are approximately equal [*i.e.*, free-energy change in the reaction ($\Delta pK$) = 0], and this finding has been confirmed by Dixon and Bruice.[4b] The exact nature of the $k_H/k_D$ maximum for these reactions has been questioned, however, by Bordwell and Boyle,[5] particularly with respect to the rate of change of $k_H/k_D$ with $\Delta pK$. Bell *et al.*[6] have also concluded from calculations based on an electrostatic model that the varying $k_H/k_D$ ratios reported by Bell and Goodall [4a] probably arise from differences of proton tunnelling rather than transition-state symmetry. These recent developments leave the utility of $k_H/k_D$ ratios as an index of transition-state symmetry in some doubt.

Aromatic hydrogen exchange, another reaction involving slow proton transfers, has been examined less thoroughly in this respect. However, varying $k_H/k_D$ ratios, but no maximum value, have often been observed for exchange of substituted benzenes in concentrated acids,[7] and more definite information is available from studies with substituted azulenes.[2c] For these compounds, Longridge and Long [2c] report a poorly-defined maximum $k_H/k_D$ in the vicinity of $\Delta pK = 0$ and, of more interest in view of Bordwell and Boyle's [5] findings, a rapidly decreasing isotope effect on either side of the maximum.

We have previously established that exchange of 3-$L_1$-2-methylindole proceeds readily by an $A$–$S_E2$ mechanism in dilute acidic buffer solutions [1] and by a concurrent general-base catalysed pathway involving

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[1] Part V, B. C. Challis and E. M. Millar, *J.C.S. Perkin II*, 1972, 1116.

[2] See (*a*) R. P. Bell, *Discuss. Faraday Soc.*, 1965, **39**, 16; (*b*) R. A. More O'Ferrall and J. Kouba, *J. Chem. Soc.* (*B*), 1967, 985; (*c*) J. L. Longridge and F. A. Long, *J. Amer. Chem. Soc.*, 1967, **89**, 1292; and (*d*) W. J. Albery, *Trans. Faraday Soc.*, 1967, **63**, 200 for references.

[3] F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265.

[4] (*a*) R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, 1966, *A*, **294**, 273; (*b*) J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, 1967, **89**, 1292; (*c*) A. J. Kresge, D. S. Sagatyo, and H. L. Chen, *J. Amer. Chem. Soc.*, 1968, **90**, 4174; (*d*) R. P. Bell and B. G. Cox, *J. Chem. Soc.* (*B*), 1970, 194.

[5] F. G. Bordwell and W. J. Boyle, *J. Amer. Chem. Soc.*, 1971, **93**, 512.

[6] R. P. Bell, W. H. Sachs, and R. L. Tranter, *Trans. Faraday Soc.*, 1971, **67**, 1995.

[7] A. J. Kresge, *Discuss. Faraday Soc.*, 1965, **39**, 49; A. C. Ling and F. H. Kendall, *J. Chem. Soc.* (*B*), 1967, 445.

the indole anion under more alkaline conditions.[8] Further, it is known that aromatic substituents may substantially alter the basicity of the 3-position.[9] In this paper, kinetic isotope effects for exchange of 3-L$_1$-indole and its 5-methoxy- and 5-cyano-derivatives are reported for several acid catalysts. These new data allow better examination of the relationship between kinetic isotope effects and transition-state symmetry for aromatic hydrogen exchange reactions.

## EXPERIMENTAL

*Substrates.*—All were obtained from commercial suppliers as unlabelled compounds; indole from B.D.H. Ltd, and 5-cyanoindole and 5-methoxyindole from the Aldrich Chemical Co. Inc. Preparation and purification of the labelled substrates has been described previously,[8] and involved either acid- or base-catalysed exchange of the 3-H with THO (The Radiochemical Centre) or $D_2O$ (Koch–Light). Specificity of the site of isotopic substitution was ascertained by combined n.m.r. and i.r. spectral examinations of the deuteriated isomers. The n.m.r. resonance for 3-H is upfield from those of other aromatic protons [10] and appeared in the range relative to tetramethylsilane $\tau$ 4·0—3·42 (1H, q) for our compounds. On deuteriation, this signal collapsed: no other change was observed apart from a decrease in the multiplicity of the 2-H and 7-H bands, corresponding to deuteriation of both 3-H and 1-H positions (the latter is a broad signal, detectable only in the integrated spectrum). Confirmation of 1-H exchange was obtained from i.r. measurements; for indole, 5-cyano-, and 5-methoxy-indole, respectively, typical N–H stretching vibrations at 3398, 3320, and 3346 cm$^{-1}$ were replaced on deuteriation with new absorption bands at 2520, 2470, and 2597 cm$^{-1}$. Dissolution of the deuteriated substrates in distilled $H_2O$ for a few minutes restored all the n.m.r. and i.r. signals assigned to 1-H, as expected from the known lability of this atom. Thus the labelling procedures introduced deuterium at only 1- and 3-positions, and the former could be removed before kinetic measurements merely by dissolving the labelled compound in $H_2O$. Since the tritiated substrates were prepared and used in an identical way, all the kinetic measurements refer to displacement of isotopic hydrogen from the 3-position only.

*Reagents.*—AnalaR pyridine and acetic, sulphuric, and perchloric acids were used without further purification. Buffer solutions were prepared from acetic acid either by partial neutralisation with B.D.H. standardised NaOH or by the addition of dried, AnalaR sodium acetate. From pyridine, buffer solutions were prepared by addition of B.D.H. standardised HCl. In both cases, the ionic strength was adjusted to 0·1 where required with AnalaR NaCl.

For the i.r. assay, reagent grade 2,2,4-trimethylpentane and carbon disulphide, and AnalaR benzene, were used without further purification.

*Kinetics.*—Protodetritiation rates were measured from the decrease in radioactivity of the substrate with respect to time by use of a liquid scintillation counting procedure. Details have been given in Parts IV [8] and V.[1]

Protodedeuteriation rates were obtained from quantitative measurements of i.r. absorptions corresponding to either C–H or C–D out-of-plane bending vibrations in the 500—800 cm$^{-1}$ region of the spectrum.[11] The method, involving extraction of the indole compound with an organic solvent from aliquot portions of reaction solution, was similar in most respects to that described earlier for experiments with 3-$^{2}$H$_1$-2-methylindole. Constant extraction for each sample was checked for 5-cyanoindole by measurement of the C≡N absorption at 2260 cm$^{-1}$ and for the other compounds by independent i.r. measurements before the kinetic studies. To obtain optimum accuracy for the i.r. assay, experimental conditions had to be carefully selected and the essential details are summarised in Table 1. With the exception of the indole absorption at 544 cm$^{-1}$ (C–D), all frequencies refer to C–H vibrational modes. Examination of independent mixtures of ordinary and deuteriated substrates showed that none of these bands was affected by neighbouring peaks, including those of isotopically substituted compounds. Concentrations of either reactant or product in each kinetic sample were interpolated from calibration plots ([InH] * or [3-$^{2}$H$_1$-InH] against log 100/% transmittance) by analysis of samples of known concentration. Calibrations were frequently checked and, where feasible, calibration and kinetic spectra were taken concurrently. It was necessary to derive actual concentrations of reactant or product as the calibration plots usually showed slight curvature.

TABLE 1

Experimental conditions for kinetic i.r. assay of 3-$^{2}$H$_1$-indoles

| Substrate | Indole | 5-Cyano-indole | 5-Methoxy-indole |
|---|---|---|---|
| Reaction scale (ml) | 100 | 500 | 100 |
| Wt substrate per expt. (mg) | 100 | 250 | 100 |
| Aliquot portion size (ml) | 10 | 50 | 10 |
| Extraction solvent | 2,2,4-Trimethylpentane | Benzene | Carbon disulphide |
| Vol. extractant (ml) | 5 | 2·5 | 3 |
| Cell pathlength and window (mm) | 3 AgCl or 2·5 NaCl | 0·65 NaCl | 1 NaCl |
| $\nu_{max.}$/cm$^{-1}$ | 720 and 544 | 775 | 756 and 720 |

Values of $k^{D}_{0}$ [equation (1)] were derived *via* the usual integrated first-order rate equation by a least-squares determination of the slope of log [3-$^{2}$H$_1$-InH] against time. For experiments with 3-$^{2}$H$_1$-indole, measurements were taken at 544 cm$^{-1}$ (C–D) and 720 cm$^{-1}$ (C–H) and for 3-$^{2}$H$_1$-5-cyanoindole at both 756 and 720 cm$^{-1}$. Rate coefficients computed from each set of data for a given compound were in good agreement.

The results for a typical experiment with 3-$^{2}$H$_1$-5-cyanoindole in 0·05M-HCl, which is representative of the accuracy attained, are given in Table 2. The error in determining protodedeuteriation rates was estimated as ±6%, about twice as large as for the detritiation experiments.

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* The symbols InH, In$^-$, and InH$_2^+$ denote the neutral indole, its conjugate base, and acid, respectively, throughout this paper.

[8] Part IV, B. C. Challis and E. M. Millar, *J.C.S. Perkin II*, 1972, 1111.

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

[10] L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Amer. Chem. Soc.*, 1960, **82**, 2184.

[11] Y. Kanaoka, Y. Ban, T. Oishi, and O. Yonemitsu, *Chem. and Pharm. Bull.*, 1960, **8**, 294.

TABLE 2

Protodedeuteriation of 3-$^2H_1$-5-cyanoindole in 0·05M-HCl at 25 °C

| Time/min | $10^3[[3\text{-}^2H_1]\text{-InH}]$/M | Reaction (%) | $10^4 k_0^D$/s$^{-1}$ |
|---|---|---|---|
| 0 | 1·32 | | |
| 5 | 1·82 | 13·8 | 4·97 |
| 10 | 2·24 | 25·3 | 4·86 |
| 20 | 2·92 | 44·2 | 4·85 |
| 30 | 3·42 | 58·0 | 4·83 |
| 45 | 3·95 | 72·6 | 4·80 |
| 60 | 4·28 | 81·8 | 4·72 |
| ∞ | 4·94 | (estimated from ν = 2260 cm$^{-1}$) | |

## RESULTS

All the exchange reactions showed a good first-order dependence on substrate concentration [equation (1)].

$$\text{Rate} = k^L_0\,[3\text{-}L_1\text{-InH}]\,^* \qquad (1)$$

Because both the neutral indole compound and its conjugate base undergo hydrogen exchange *via* $S_E2$ pathway,[1,8] $k^L_0$ is comprised of contributions from all acid and base catalysts in the reaction solution. Its general relationship to second-order rate coefficients is equation (2), where $HA_i$ and $B_j$ refer to acid and base-catalysts, respectively, and $k^L_{H_2O}[H_2O]$ is the spontaneous water rate. In practice it is usually possible to minimise contributions from both base

$$k^L_0 = \sum_i k^L_{HA_i}[HA_i] + \sum_j k^L_{B_j}[B_j] + k^L_{H_2O}[H_2O] \qquad (2)$$

catalysts and the solvent by careful selection of the experimental conditions.

*Acetic Acid Buffers.*—It can be deduced from previous studies[1,8] that at pH < 5, neither $OH^-$ nor $H_2O$ make significant contributions to the overall rate. Thus the effective second-order relationship for exchange in acetic acid buffers is given by equation (3). Values of $k^L_0$ for

$$k^L_0 = k^L_{H_3O^+}[H_3O^+] + k^L_{HOAc}[HOAc] + k^L_{AcO^-}[AcO^-] \qquad (3)$$

protodetritiation and protodedeuteriation of all three compounds are listed in Tables 3—7. These refer to sets of experiments where the buffer ratios ([HOAc]/[AcO$^-$]), and therefore the [H$_3$O$^+$], is constant, and, for all but 3-$^2H_1$-5-cyanoindole, data are reported for two different buffer ratios. Thus second-order catalytic coefficients have been evaluated from linear plots of $k^L_0$ against [HOAc], where the intercept = $k^L_{H_3O^+}[H_3O^+]$ and the slope = $k^L_{HOAc} + k^L_{AcO^-}[AcO^-]/[HOAc]$.

TABLE 3

Protodetritiation of 3-$^3H_1$-indole in acetic acid buffers [a] at 25 °C

| $10^2$[HOAc]/M | $10^2$[NaOAc]/M | $10^5 k^T_0$/s$^{-1}$ |
|---|---|---|
| 10·0 | 10·0 | 5·27 (5·73) [b] |
| 7·50 | 7·50 | 4·66 |
| 5·00 | 5·00 | 3·56 (3·63) |
| 2·50 | 2·50 | 2·50 |
| 1·00 | 1·00 | 1·79 (1·82) |

$k^T_{HOAc} = 4{\cdot}33 \times 10^{-4}$ l mol$^{-1}$ s$^{-1}$
$k^T_{H_3O^+} = 0{\cdot}502$ l mol$^{-1}$ s$^{-1}$

| $10^2$[HOAc]/M | $10^2$[NaOAc]/M | $10^5 k^T_0$/s$^{-1}$ |
|---|---|---|
| 3·33 | 10·0 | 1·94 |
| 2·50 | 7·50 | 1·55 |
| 1·67 | 5·00 | 1·19 |
| 0·833 | 2·50 | 0·84 |
| 0·333 | 1·00 | 0·61 |

$k^T_{HOAc} = 4{\cdot}35 \times 10^{-4}$ l mol$^{-1}$ s$^{-1}$
$k^T_{H_3O^+} = 0{\cdot}505$ l mol$^{-1}$ s$^{-1}$

[a] μ = 0·10 by addition of NaCl. [b] Duplicate experiments in parentheses.

TABLE 4

Protodetritiation of 3-$^3H_1$-5-methoxyindole in acetic acid buffers [a] at 25 °C

| $10^2$[HOAc]/M | $10^2$[NaOAc]/M | $10^5 k^T_0$/s$^{-1}$ |
|---|---|---|
| 10·0 | 10·0 | 15·4 |
| 7·50 | 7·50 | 12·5 |
| 5·00 | 5·00 | 9·25 |
| 2·50 | 2·50 | 6·35 |
| 1·00 | 1·00 | 4·25 |

$k^T_{HOAc} = 1{\cdot}21 \times 10^{-3}$ l mol$^{-1}$ s$^{-1}$
$k^T_{H_3O^+} = 1{\cdot}18$ l mol$^{-1}$ s$^{-1}$

| $10^2$[HOAc]/M | $10^2$[NaOAc]/M | $10^5 k^T_0$/s$^{-1}$ |
|---|---|---|
| 50·0 | 10·0 | 7·62 |
| 40·0 | 8·00 | 6·45 |
| 30·0 | 6·00 | 5·02 |
| 15·0 | 3·00 | 3·40 |
| 5·00 | 1·00 | 2·14 |

$k^T_{HOAc} = 1{\cdot}22 \times 10^{-3}$ l mol$^{-1}$ s$^{-1}$
$k^T_{H_3O^+} = 1{\cdot}09$ l mol$^{-1}$ s$^{-1}$

[a] μ = 0·10 by addition of NaCl.

TABLE 5

Protodedeuteriation of 3-$^2H_1$-indole in acetic acid buffers [a] at 25 °C

| $10^2$[HOAc]/M | $10^2$[NaOAc]/M | $10^5 k^D_0$/s$^{-1}$ |
|---|---|---|
| 10·0 | 10·0 | 10·9 (11·5) [b] |
| 7·50 | 7·50 | 9·05 |
| 5·00 | 5·00 | 7·00 (7·10) |
| 2·50 | 2·50 | 5·00 |
| 1·00 | 1·00 | 3·62 |

$k^D_{HOAc} = 8{\cdot}39 \times 10^{-4}$ l mol$^{-1}$ s$^{-1}$
$k^D_{H_3O^+} = 1{\cdot}00$ l mol$^{-1}$ s$^{-1}$

| $10^2$[HOAc]/M | $10^2$[NaOAc]/M | $10^5 k^D_0$/s$^{-1}$ |
|---|---|---|
| 3·33 | 10·0 | 3·60 |
| 2·50 | 7·50 | 3·10 |
| 1·67 | 5·00 | 2·40 |
| 0·833 | 2·50 | 1·64 |
| 0·333 | 1·00 | 1·22 |

$k^D_{HOAc} = 8{\cdot}22 \times 10^{-4}$ l mol$^{-1}$ s$^{-1}$
$k^D_{H_3O^+} = 1{\cdot}03$ l mol$^{-1}$ s$^{-1}$

[a] μ = 0·10 by addition of NaCl. [b] Duplicate experiments in parentheses.

TABLE 6

Protodedeuteriation of 3-$^2H_1$-5-methoxyindole in acetic acid buffers [a] at 25 °C

| $10^2$[HOAc]/M | $10^2$[NaOAc]/M | $10^4 k^D_0$/s$^{-1}$ |
|---|---|---|
| 50·0 | 10·0 | 15·7 |
| 40·0 | 8·00 | 13·1 |
| 30·0 | 6·00 | 10·5 |
| 15·0 | 3·00 | 7·55 |
| 5·00 | 1·00 | 4·78 |

$k^D_{HOAc} = 2{\cdot}45 \times 10^{-3}$ l mol$^{-1}$ s$^{-1}$
$k^D_{H_3O^+} = 2{\cdot}50$ l mol$^{-1}$ s$^{-1}$

| $10^2$[HOAc]/M | $10^2$[NaOAc]/M | $10^4 k^D_0$/s$^{-1}$ |
|---|---|---|
| 10·0 | 10·0 | 328 |
| 7·50 | 7·50 | 254 |
| 5·00 | 5·00 | 191 |
| 2·50 | 2·50 | 124 |
| 1·00 | 1·00 | 82·0 |

$k^D_{HOAc} = 2{\cdot}57 \times 10^{-3}$ l mol$^{-1}$ s$^{-1}$
$k^D_{H_3O^+} = 2{\cdot}15$ l mol$^{-1}$ s$^{-1}$

[a] μ = 0·10 by addition of NaCl.

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* Throughout the text, L refers to either tritium or deuterium as appropriate.

Within the limits of experimental error (∓2%), the slope of these plots for 5-methoxyindole and indole itself are independent of the buffer ratio, which shows that, to a good approximation, any contribution from the acetate ion catalyst can also be disregarded. Values of $k^{\mathrm{L}}_{\mathrm{H_3O^+}}$ and $k^{\mathrm{L}}_{\mathrm{HOAc}}$ obtained by a ' least-squares ' analysis of the data by assuming $K_{\mathrm{HOAc}} = 2{\cdot}79 \times 10^{-5}$ mol l$^{-1}$,[12] are given at the foot of each set of experimental results. The agreement between equivalent coefficients is satisfactory.

TABLE 7

Hydrogen exchange of 3-L$_1$-5-cyanoindoles in acetic acid buffers [a] at 25 °C

| $10^2$[HOAc]/M | $10^2$[NaOAc]/M | $10^7k^{\mathrm{L}}_0$/s$^{-1}$ |
|---|---|---|
| Protodetritiation | | |
| 50·0 | 10·0 | 27·6 |
| 40·0 | 8·00 | 23·8 |
| 30·0 | 6·00 | 19·9 |
| 15·0 | 3·00 | 13·5 |
| 5·00 | 1·00 | 9·71 |
| 20·0 | 10·0 | 11·6 |
| 16·0 | 8·00 | 9·90 |
| 12·0 | 6·00 | 7·80 |
| Protodedeuteriation | | |
| 50·0 | 10·0 | 52·5 |
| 40·0 | 8·00 | 50·2 |
| 30·0 | 6·00 | 40·8 |
| 15·0 | 3·00 | 26·8 |
| 5·00 | 1·00 | 19·3 |

[a] μ = 0·10 by addition of NaCl.

For protodetritiation of 3-$^3$H$_1$-5-cyanoindole, the least-squares slopes of $k^{\mathrm{L}}_0$ against [HOAc] plots differ by 6%, which is slightly larger than the estimated error and indicative of small, but significant, AcO$^-$ catalysis. Perhaps this is not surprising, as 5-cyanoindole is the most acidic compound studied. Solution of the relevant simultaneous equations (4) and (5), derived from the two slope measurements, leads to values of $k^{\mathrm{T}}_{\mathrm{HOAc}} = 3{\cdot}87(\mp 0{\cdot}07) \times 10^{-6}$ l mol$^{-1}$ s$^{-1}$ and $k^{\mathrm{T}}_{\mathrm{AcO^-}} = 8{\cdot}7(\pm 2{\cdot}5) \times 10^{-7}$ l mol$^{-1}$ s$^{-1}$. The intercept of the plot for the higher buffer ratio gives $k^{\mathrm{T}}_{\mathrm{H_3O^+}} = 5{\cdot}36 \times 10^{-3}$ l mol$^{-1}$ s$^{-1}$.

$$k^{\mathrm{T}}_{\mathrm{HOAc}} + 0{\cdot}2k^{\mathrm{T}}_{\mathrm{AcO^-}} = 4{\cdot}04 \times 10^{-6} \tag{4}$$

$$k^{\mathrm{T}}_{\mathrm{HOAc}} + 0{\cdot}5k^{\mathrm{T}}_{\mathrm{AcO^-}} = 4{\cdot}30 \times 10^{-6} \tag{5}$$

The corresponding protodedeuteriation of 3-$^2$H$_1$-5-cyanoindole was examined only in a single set of buffers with [HOAc]/[AcO$^-$] = 5 (see Table 7), but an estimate can be made for catalysis by AcO$^-$ to derive $k^{\mathrm{D}}_{\mathrm{HOAc}}$ from these data. As for protodetritiation, a ' least squares ' analysis leads to equation (6) for catalysis by the buffer components. From direct studies of base-catalysed exchange (see following paper) the value of $k^{\mathrm{D}}_{\mathrm{AcO^-}}/k^{\mathrm{T}}_{\mathrm{AcO^-}}$ may be placed in the range 1·25—2·5. Since $k^{\mathrm{T}}_{\mathrm{AcO^-}} = 8{\cdot}7 \times 10^{-7}$ l mol$^{-1}$ s$^{-1}$, $k^{\mathrm{D}}_{\mathrm{AcO^-}}$ will lie between 1·09 and 2·18 × 10$^{-6}$ l mol$^{-1}$ s$^{-1}$. Substitution in equation (6) then gives $k^{\mathrm{D}}_{\mathrm{HOAc}} = 7{\cdot}79(\pm 0{\cdot}51) \times 10^{-6}$ l mol$^{-1}$ s$^{-1}$.

$$k^{\mathrm{D}}_{\mathrm{HOAc}} + 0{\cdot}2k^{\mathrm{D}}_{\mathrm{AcO^-}} = 8{\cdot}12(\pm 0{\cdot}4) \times 10^{-6} \tag{6}$$

*Hydrochloric Acid.*—For indole and 5-cyanoindole, exchange rates could be accurately measured in dilute HCl to give $k^{\mathrm{L}}_{\mathrm{H_3O^+}}$ directly from equation (7).

$$\text{Rate} = k^{\mathrm{L}}_{\mathrm{H_3O^+}}[3\text{-L}_1\text{-InH}][\mathrm{HCl}] \tag{7}$$

These results are listed in Table 8. Indole was examined at only a single dilute [HCl], but these runs were repeated and a mean value taken. Agreement between $k^{\mathrm{L}}_{\mathrm{H_3O^+}}$ obtained in this way and from experiments in acetic acid buffers is generally excellent. This vindicates the assumption of a negligible solvent and OH$^-$-catalysed contribution to the rate in the buffer solutions.

TABLE 8

Hydrogen exchange rates of 3-L$_1$-indoles in dilute HCl [a] at 25 °C

| $10^2$[HCl]/M | $10^5k^{\mathrm{L}}_0$/s$^{-1}$ [b] |
|---|---|
| 3-$^3$H$_1$-5-Cyanoindole | |
| 10 | 51·5 (53·2) |
| 5·0 | 26·3 (26·4) |
| 1·0 | 5·23 |
| 3-$^2$H$_1$-5-Cyanoindole | |
| 10 | 93·5 |
| 5·0 | 48·4 |
| 1·0 | 10·8 (9·5) |
| 3-$^3$H$_1$-Indole | |
| 0·481 | 239 (241) |
| 3-$^2$H$_1$-Indole | |
| 0·10 | 97·9 (97·2, 97·3) |

[a] μ = 0·10 by addition of NaCl. [b] Duplicate measurements in parentheses.

TABLE 9

Protodetritiation of 3-$^3$H$_1$-indole in pyridine buffers [a] at 25 °C

| $10^2$[C$_5$H$_5$N]/M | $10^2$[C$_5$H$_5$NH$^+$Cl$^-$]/M | $10^6k^{\mathrm{T}}_0$/s$^{-1}$ |
|---|---|---|
| 60 | 10 | 14·6 |
| 42 | 7·0 | 10·4 |
| 24 | 4·0 | 6·42 |
| 6·0 | 1·0 | 1·82 |
| Slope $k^{\mathrm{T}}_{\mathrm{C_5H_5NH^+Cl^-}} + 6k^{\mathrm{T}}_{\mathrm{C_5H_5N}} = 14{\cdot}1 \times 10^{-5}$ l mol$^{-1}$ s$^{-1}$ | | |
| 30 | 10 | 13·5 |
| 21 | 7·0 | 9·71 |
| 12 | 4·0 | 6·45 |
| 3·0 | 1·0 | 2·21 |
| Slope $k^{\mathrm{T}}_{\mathrm{C_5H_5NH^+Cl^-}} + 3k^{\mathrm{T}}_{\mathrm{C_5H_5N}} = 12{\cdot}2 \times 10^{-5}$ l mol$^{-1}$ s$^{-1}$ | | |
| 5·0 | 10 | 16·2 |
| 3·75 | 7·5 | 13·7 |
| 2·5 | 5·0 | 11·1 |
| 1·5 | 3·0 | 9·06 |
| 0·50 | 1·0 | 6·54 |
| Slope $k^{\mathrm{T}}_{\mathrm{C_5H_5NH^+Cl^-}} + 0{\cdot}5k^{\mathrm{T}}_{\mathrm{C_5H_5N}} = 10{\cdot}3 \times 10^{-5}$ l mol$^{-1}$ s$^{-1}$ | | |

[a] μ = 0·1 by addition of NaCl.

*Pyridine Buffers.*—The exchange reactions of 3-L$_1$-indole were also investigated in aqueous pyridine buffer solutions at three different buffer ratios ([C$_5$H$_5$NH$^+$Cl$^-$]/[C$_5$H$_5$N]) and values of $k^{\mathrm{L}}_0$ are given in Tables 9 and 10 for protodetritiation and dedeuteriation, respectively. Second-order rate coefficients have been deduced as previously described, it being assumed that both the ' spontaneous ' water and OH$^-$-catalysed rates are negligible, by means of equation (8).

$$k^{\mathrm{L}}_0 = k^{\mathrm{L}}_{\mathrm{H_3O^+}}[\mathrm{H_3O^+}] + k^{\mathrm{L}}_{\mathrm{C_5H_5NH^+Cl^-}}[\mathrm{C_5H_5NH^+Cl^-}] + k^{\mathrm{L}}_{\mathrm{C_5H_5N}}[\mathrm{C_5H_5N}] \tag{8}$$

It is apparent from plots of $k^{\mathrm{L}}_0$ against [C$_5$H$_5$NH$^+$Cl$^-$] that account must be taken of catalysis by neutral pyridine (see

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[12] M. Kilpatrick and R. D. Eanes, *J. Amer. Chem. Soc.*, **1953**, **75**, 586.

Figure 1). Solution of the relevant simultaneous equations derived from a ' least-squares ' determination of the slope for each plot (the equation is given at the foot of each set of data) leads to the following values (in l mol$^{-1}$ s$^{-1}$) for these coefficients: $k^{T}{}_{C_5H_5NH^+Cl^-} = 10{\cdot}1(\pm 0{\cdot}2) \times 10^{-5}$; $k^{T}{}_{C_5H_5N} = 6{\cdot}9(\pm 0{\cdot}5) \times 10^{-6}$; $k^{D}{}_{C_5H_5NH^+Cl^-} = 17{\cdot}8(\pm 1{\cdot}0) \times 10^{-5}$; $k^{D}{}_{C_5H_5N} = 17{\cdot}9(\pm 2{\cdot}6) \times 10^{-6}$.

TABLE 10

Protodedeuteriation of 3-$^2H_1$-indole in pyridine buffers [a] at 25 °C

| $10^2[C_5H_5N]$/M | $10^2[C_5H_5NH^+Cl^-]$/M | $10^6k^D{}_0$/s$^{-1}$ |
|---|---|---|
| 60 | 10 | 28·2 |
| 42 | 7·0 | 19·7 |
| 24 | 4·0 | 11·0 |
| 15 | 2·5 | 6·86 |
| 6·0 | 1·0 | 3·35 |
| Slope $k^D{}_{C_5H_5NH^+Cl^-} + 6k^D{}_{C_5H_5N} = 27{\cdot}8 \times 10^{-5}$ l mol$^{-1}$ s$^{-1}$ | | |
| 30 | 10 | 25·3 |
| 24 | 8·0 | 19·8 |
| 18 | 6·0 | 15·3 |
| 12 | 4·0 | 10·7 |
| 3·0 | 1·0 | 3·90 |
| Slope $k^D{}_{C_5H_5NH^+Cl^-} + 3k^D{}_{C_5H_5N} = 23{\cdot}5 \times 10^{-5}$ l mol$^{-1}$ s$^{-1}$ | | |
| 5·0 | 10 | 29·5 |
| 3·75 | 7·5 | 25·9 |
| 2·5 | 5·0 | 22·0 |
| 1·5 | 3·0 | 17·5 |
| 0·50 | 1·0 | 13·3 |
| Slope $k^D{}_{C_5H_5NH^+Cl^-} + 0{\cdot}5k^D{}_{C_5H_5N} = 18{\cdot}1 \times 10^{-5}$ l mol$^{-1}$ s$^{-1}$ | | |

[a] $\mu = 0{\cdot}1$ by addition of NaCl.

Consideration of additional catalytic terms to equation (8), such as $k^L[C_5H_5NH^+Cl^-][C_5H_5N]$ for simultaneous catalysis by pyridine and its conjugate acid, does not provide a satisfactory solution to the simultaneous equations. We therefore presume that this pathway is unimportant. Also, values of $k^L{}_{H_3O^+}$ derived from the intercepts of $k^L{}_0$ against $[C_5H_5NH^+Cl^-]$, p$K_A$ being assumed to be 5·18 for $C_5H_5NH^+Cl^-$ in 0·1M-salt solution,[13] are in satisfactory agreement with those obtained from the other measurements.

## DISCUSSION

Hydrogen exchange of 3-$L_1$-2-methylindoles, in common with other, relatively basic, aromatic species, occurs by an *A*–$S_E2$ pathway.[1] No radical change of mechanism should arise from the modifications to substrate structure occasioned by the present investigation, and this is borne out by the observation of general acid catalysis and of substantial kinetic isotope effects, salient characteristics of the *A*–$S_E2$ mechanism for all three compounds. The incidence of general base catalysis under certain experimental conditions is a peculiarity of indole compounds arising from reaction of the conjugate base species.[8] It is not an important pathway at low pH and we shall not be concerned further with this aspect of the reaction here.

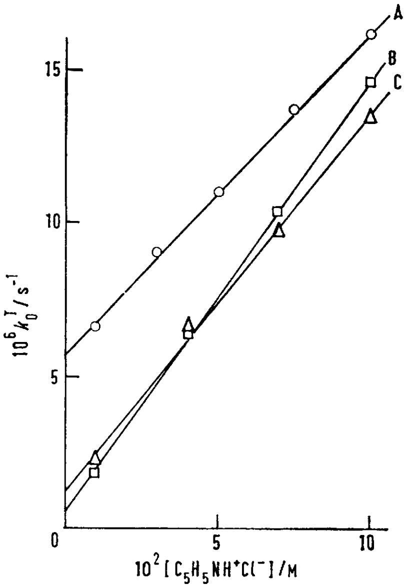
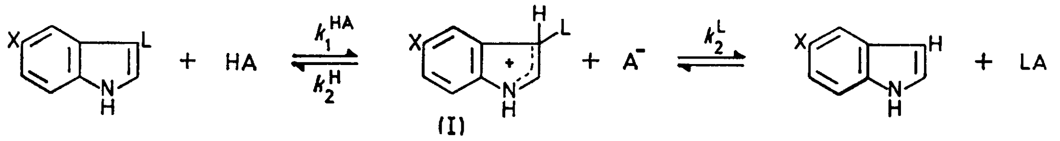


FIGURE 1 Protodetritiation of 3-$^3H_1$-indole in pyridine buffer solutions at 25 °C, buffer ratios: A, 2; B, 0·667; C, 0·333

The *A*–$S_E2$ mechanism (Scheme) involves the neutral substrate and proceeds *via* the relatively stable conjugate acid intermediate (I). The symbol HA represents the acid catalyst, in this case $H_3O^+$, HOAc, or $C_5H_5NH^+$. Although the process is fully reversible, under our kinetic conditions with low substrate concentrations (<$10^{-2}$M) the reverse rate to $k^L{}_2$ is effectively zero because the concentration of isotopic species (LA) is also very low. The other three steps in the Scheme are all kinetically significant. Their relationship to the second-order catalytic coefficients ($k^L{}_{H_3O^+}$, $k^L{}_{HOAc}$, *etc.*) has been discussed,[1] and is given for the general case by equation (9).



SCHEME A–$S_E2$ Mechanism for hydrogen exchange of 3-$L_1$-indoles

$$k^L{}_{HA} = \frac{k^{HA}{}_1}{1 + k^H{}_2/k^L{}_2} \qquad (9)$$

It is the isotopic rate ratios ($k^H{}_2/k^L{}_2$) that are of prime interest. They cannot be deduced directly from the experimental data for a single reaction and we have followed the procedure used previously for 3-$L_1$-2-methylindole whereby $k^H{}_2/k^D{}_2$ ratios are calculated by solution of simultaneous expressions from protodetritiation and protodedeuteriation [equations (10) and (11), respectively] on the assumption that $k^H{}_2/k^T{}_2 = (k^H{}_2/k^D{}_2)^{1{\cdot}442}$.[1] The

[13] C. J. Hawkins and D. D. Perrin, *J. Chem. Soc.*, 1962, 1351.

best experimental data for these calculations and the isotopic rate ratios obtained are summarised in Table 11

$$k^{\mathrm{T}}{}_{\mathrm{HA}} = \frac{k^{\mathrm{HA}}{}_1}{1 + (k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2)^{1\cdot442}} \qquad (10)$$

$$k^{\mathrm{D}}{}_{\mathrm{HA}} = \frac{k^{\mathrm{HA}}{}_1}{1 + k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2} \qquad (11)$$

together with $\mathrm{p}K_{\mathrm{A}}$ values (in parentheses) of both substrates and catalysts. Values reported[1] for 3-$L_1$-2-methylindoles are also given for comparison. All the ratios are substantial and no obvious trend is apparent, but this point will be taken up later.

It should be noted that $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ ratios in Table 11 comprise both a primary and secondary hydrogen isotope effect. The latter arises from both the formation ($k_1$) and breakdown ($k_2$) steps of the intermediate (I) and neither is allowed for in deriving equations 10 and 11. They are not insignificant and may be as large as 15%. Kresge and Chiang[14] have shown from studies of trimethoxybenzene that allowance for these secondary isotope effects increases the $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ ratios substantially. Thus the values in Table 11 should be regarded as *minimum* primary isotope effects for the hydrogen exchange reactions. Nonetheless, the cited $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ ratios represent from 58 to 81% of the predicted maximum of 7·8 based on a simple consideration of zero-point energy differences for a C–H stretching vibration of 2900 cm$^{-1}$ for a methylene group. As far as the following discussion is concerned, relative, rather than absolute, primary isotope effects are important, and in this context it seems unlikely that any secondary effects, arising primarily from change of hybridisation ($sp^3 \longleftrightarrow sp^2$) at the reactive 3-position, will be strongly dependent on substituent effects at remote dispositions. Thus $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ ratios in Table 11 can be compared directly, and this comparison can probably be extended to the data for other aromatic hydrogen exchange reactions computed by a similar procedure.

TABLE 11

Second-order rate coefficients and kinetic isotope effects for hydrogen exchange of 3-$L_1$-X-indoles at 25 °C ($k^{\mathrm{T}}{}_{\mathrm{HA}}$ and $k^{\mathrm{D}}{}_{\mathrm{HA}}$ in l mol$^{-1}$ s$^{-1}$)

| Substituent[a] X | Catalyst[a] (HA) | $k^{\mathrm{T}}{}_{\mathrm{HA}}$ | $k^{\mathrm{D}}{}_{\mathrm{HA}}$ | $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ | $\Delta pK$[b] |
|---|---|---|---|---|---|
| 2-Me (−0·28)[c] | $H_3O^+$ (−1·75) | 40·8[e] | 85·0[e] | 6·3 ± 1·0 | +1·47 |
| 5-MeO (−2·9)[d] | $H_3O^+$ (−1·75) | 1·14 | 2·33 | 6·0 ± 1·2 | −1·15 |
| 5-H (−3·5)[c] | $H_3O^+$ (−1·75) | 0·50 | 0·97 | 5·6 ± 0·3 | −1·75 |
| 5-CN (−6·0)[d] | $H_3O^+$ (−1·75) | $5{\cdot}27 \times 10^{-3}$ | $9{\cdot}8 \times 10^{-3}$ | 5·0 ± 0·7 | −4·25 |
| 2-Me | HOAc (4·76) | $6{\cdot}9 \times 10^{-2}$[e] | $14{\cdot}4 \times 10^{-2}$[e] | 6·3 ± 1·0 | −5·04 |
| 5-MeO | HOAc (4·76) | $1{\cdot}22 \times 10^{-3}$ | $2{\cdot}51 \times 10^{-3}$ | 6·2 ± 0·6 | −7·66 |
| 5-H | HOAc (4·76) | $4{\cdot}34 \times 10^{-4}$ | $8{\cdot}3 \times 10^{-4}$ | 5·3 ± 0·4 | −8·26 |
| 5-CN | HOAc (4·76) | $3{\cdot}87 \times 10^{-6}$ | $7{\cdot}8 \times 10^{-6}$ | 5·9 ± 0·9 | −10·76 |
| 5-H | $C_5H_5NH^+Cl^-$ (5·25) | $1{\cdot}01 \times 10^{-4}$ | $1{\cdot}78 \times 10^{-4}$ | 4·5 ± 0·8 | −8·75 |

[a] pK in parentheses. [b] $\Delta\mathrm{p}K = \mathrm{p}K_{\mathrm{substrate}} - \mathrm{p}K_{\mathrm{catalyst}}$. [c] Ref. 9. [d] Ref. 20. [e] Ref. 1.

*Transition-state Symmetry.*—Following the procedure of Bell and Goodall[4a] and Longridge and Long[2c] we have taken $\Delta\mathrm{p}K$ ($= \mathrm{p}K_{\mathrm{substrate}} - \mathrm{p}K_{\mathrm{catalyst}}$) as an index of transition-state symmetry for the hydrogen exchange and these parameters are included in Table 11. The most noticeable feature of our data is that little change of $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ is found over 12 units of $\Delta\mathrm{p}K$; a 'least-squares' analysis shows that $\mathrm{d}(k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2)/\mathrm{d}\Delta\mathrm{p}K = ca.\ -0{\cdot}06$. This slope is in the direction predicted by theoretical arguments,[2] but it is very much smaller than those reported for most other investigations. There is, further, no clear indication that $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ passes through a maximum at $\Delta\mathrm{p}K = 0$. However, one of the largest $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ ratios (for $H_3O^+$-catalysed exchange of 3-$L_1$-2-methylindole) is close to $\Delta\mathrm{p}K = 0$ and most of the results refer to negative values of $\Delta\mathrm{p}K$.

It is instructive to examine how well these findings correlate with other investigations of aromatic hydrogen exchange. With this in mind, $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ ratios for several azulenes reported by Longridge and Long,[2c] and for trimethoxybenzene studied both by Kresge and Chiang[15] and Batts and Gold[16] are plotted against $\Delta\mathrm{p}K$ in Figure 2, together with those for the indole compounds. All known reliable values for $A$–$S_{\mathrm{E}2}$ exchange reactions are included (omitted are one uncertain datum for 4,6,8-trimethylazulene[2c] and several results[7] for feebly basic compounds of unknown p$K$). None of these ratios is corrected for secondary isotope effects.

The scatter of points in Figure 2 is considerable but not entirely unexpected. Apart from inaccuracies in the experimental methods, the neglect of secondary isotope effects, tunnelling and specific steric interactions is a major simplification and all may alter $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ ratios. Nonetheless, any conclusion that $k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2$ is strongly dependent on $\Delta\mathrm{p}K$ relies almost entirely on the large ratio for the $H_3O^+$-catalysed exchange of azulene ($k^{\mathrm{H}}{}_2/k^{\mathrm{D}}{}_2 = 9{\cdot}2$),[2c] whereas the remaining data are close to the 'least-squares' line derived from the indole results.

Remarkably similar findings of relatively constant primary isotope effects have been reported recently by Bordwell and Boyle[5] for proton abstraction from 1-arylnitroethanes. Coupled with our observations, there is a strong inclination to regard this kind of behaviour as normal for all proton transfer processes. Other results are contradictory, however, and there is

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[14] A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, 1967, **89**, 4411.

[15] A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, 1962, **84**, 3976.

[16] B. D. Batts and V. Gold, *J. Chem. Soc.*, 1964, 4284.

good evidence that primary isotope effects even for aromatic substitution can be strongly dependent on $\Delta pK$, as in the diazo-coupling of 1-hydroxynaphthalene-2-sulphonic acids.[17] We have therefore looked for some special factor that might diminish changes in $k^{\mathrm{H}}_2/k^{\mathrm{D}}_2$ for aromatic hydrogen exchange. An obvious, yet apparently unsatisfactory, possibility is that proton donation and removal from the conjugate acid intermediate (I) is synchronous, or at least partially so. This interaction should be more significant for bifunctional catalysts such as carboxylic acids and it is these data, in particular, that generate the low slope of Figure 2, whereas consideration of only the $H_3O^+$-catalysed reactions produces a larger change of $k^{\mathrm{H}}_2/k^{\mathrm{D}}_2$ with $\Delta pK$. Other evidence, however, suggests this particular difference is fortuitous. Thus carboxylic acids (as far as Brønsted plots are concerned) show no special catalytic properties [18] and, further, $k^{\mathrm{H}}_2/k^{\mathrm{D}}_2$ for $C_5H_5NH^+$ catalysed exchange of 3-$L_1$-indole is almost as large as that for acetic acid catalysis.

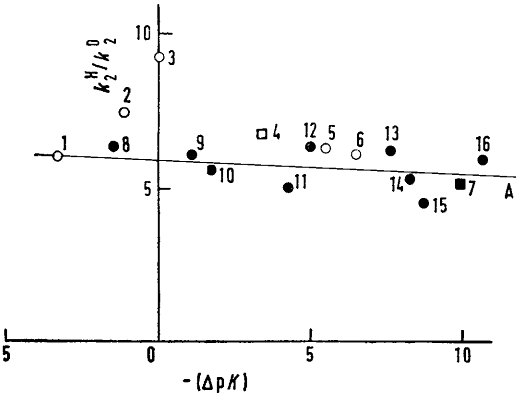

FIGURE 2 $k^{\mathrm{H}}_2/k^{\mathrm{D}}_2$ Ratios as a function of $-(\Delta pK)$ for $A$-$S_E2$ aromatic hydrogen exchange reactions; 1, guaiazulene–$H_3O^+$; 2; guaiazulene sulphonate–$H_3O^+$; 3, azulene–$H_3O^+$; 4, trimethoxybenzene–$H_3O^+$; 5, azulene–$HCO_2H$; 6, azulene–HOAc; 7, trimethoxybenzene–HOAc; 8, 2-methylindole–$H_3O^+$; 9, 5-methoxyindole–$H_3O^+$; 10, indole–$H_3O^+$; 11, 5-cyanoindole–$H_3O^+$; 12, 2-methylindole–HOAc; 13, 5-methoxyindole–HOAc; 14, indole–HOAc; 15, indole–$C_5H_5NH^+$; 16, 5-cyanoindole–HOAc; ●, this work; ○, ref. 2*c*; ■, ref. 14 and 16; the line A is the 'least-squares' line for the results for indoles

It is conceivable, too, that the extent of proton transfer varies little over the range of $\Delta pK$ examined in Figure 2 and remarkably similar median Brønsted exponents reported for general acid-catalysed exchange of at least three of the substrates (azulene, $\alpha \simeq 0{\cdot}67$;[18b] trimethoxybenzene, $\alpha \simeq 0{\cdot}52$;[18c] and 2-methylindole, $\alpha \simeq 0{\cdot}46$ [18a]) are consistent with this hypothesis. Examination of several aliphatic reactions, however, has shown the Brønsted exponent to be an unreliable index of transition state structure,[19] and the same uncertainty is evident for aromatic hydrogen exchange. Two Brønsted plots derived from $k^{\mathrm{T}}_{\mathrm{HA}}$ values listed in Table 11, supplemented with additional data for 3-$^3H_1$-6-nitroindole, $pK_{\mathrm{InH_2^+}} = -6{\cdot}9$,[9] ($k^{\mathrm{T}}_{\mathrm{H_3O^+}} = 2{\cdot}75 \times 10^{-3}$ l mol$^{-1}$ s$^{-1}$) and 3-$^3H_1$-2-t-butylindole, $pK_{\mathrm{InH_2^+}} = -0{\cdot}80$,[20] ($k^{\mathrm{T}}_{\mathrm{H_3O^+}} = 31{\cdot}9$ l mol$^{-1}$ s$^{-1}$, $k^{\mathrm{T}}_{\mathrm{HOAc}} = 4{\cdot}2 \times 10^{-2}$ l mol$^{-1}$ s$^{-1}$) are shown in Figure 3. Each line refers to either $H_3O^+$ or HOAc-catalysed exchange of different indole substrates, including 3-$^3H_1$-2-methylindole, and their slopes correspond to values of $\beta = 0{\cdot}67$ and $\beta = 0{\cdot}75$, respectively. Both are significantly different from the equivalent Brønsted exponent ($\alpha = 0{\cdot}46$) found for exchange of 3-$^3H_1$-2-methylindole by variation of the acid catalyst.[18a] The exact significance of either $\alpha$ or $\beta$ values to the degree of proton transfer in the transition state is therefore uncertain and deductions based on any similarity of $\alpha$ values for different types of substrate may be misleading.

It does appear that $k^{\mathrm{H}}_2/k^{\mathrm{D}}_2$ ratios, and probably primary isotope effects, too, are largely insensitive to $\Delta pK$ for aromatic hydrogen exchange or that the observation of substantially sub-maximum $k^{\mathrm{H}}_2/k^{\mathrm{D}}_2$ ratios requires, at least, a much larger difference of substrate and catalyst reactivity than is usually employed. Whether or not this reflects a relatively constant extent of proton transfer in their transition states, or that primary hydrogen isotope effects are almost independent of transition-state structure, is not clear. There is no evidence for proton tunnelling in these reactions, however, and the results are entirely consistent with this factor being of major importance to the incidence of varying primary isotope effects.

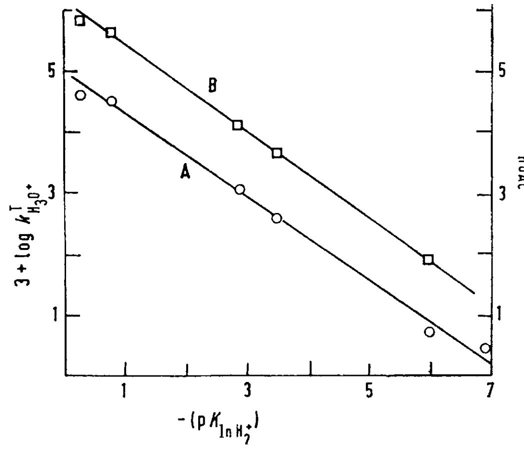

FIGURE 3 Brønsted plots for A, $H_3O^+$- and B, HOAc-catalysed protodetritiation of 3-$^3H_1$-indoles at 25 °C

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[2/167 *Received, 27th January*, 1972]

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