Heteroaromatic Hydrogen Exchange Reactions. Part V.[1] Isotope Effects for the Acid-catalysed Exchange of 3-^3H_1-2-Methylindole and 3-^2H_1-2-Methylindole

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Hydrogen exchange rates are reported for 2-methylindoles labelled with either deuterium or tritium at the 3-position in a range of acetic acid buffer solutions at 25 °C prepared in either H_2O or D_2O. Various isotopic rate ratios calculated from these data are entirely consistent with an $A\text{-}S_E2$ mechanism for the hydrogen exchange, in which the proton is approximately half-transferred to the substrate in the transition state.

THE usual $A\text{-}S_E2$ mechanism for aromatic hydrogen exchange is characterised by the incidence of general-acid catalysis, reaction *via* a conjugate acid intermediate, and substantial primary hydrogen isotope effects.[2] For relatively basic compounds such as azulenes[3] and aromatic ethers,[4] $k_H : k_D$ ratios are in the range 5—9; their large magnitudes are thought to indicate fairly symmetrical transition states for the proton transfer and this accords with Brønsted exponents (α) for general-acid catalysis close to 0·5.

The indole nucleus is susceptible to electrophilic substitution in mildly acidic or neutral media at position 3.[5] Protonation occurs at this site too, and the basicity of several compounds (including 2-methylindole) has been measured.[6] These facts, together with our earlier observation[7] of general-acid catalysis for the protodetritiation of 3-^3H_1-2-methylindole point to an $A\text{-}S_E2$ exchange mechanism. The observation of coherent hydrogen isotope effects would therefore be powerful confirmation of this. Accordingly we now compare the exchange rates of $3\text{-}L_1$-2-methylindoles † in a range of aqueous acetic acid buffer solutions.

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† Throughout the paper L refers to either tritium or deuterium as appropriate.

[1] Part IV, B. C. Challis and E. M. Millar, preceding paper.

[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 and Y. Chiang, *J. Amer. Chem. Soc.*, 1967, **89**, 4411 and references therein.

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

[7] Part II, B. C. Challis and F. A. Long, *J. Amer. Chem. Soc.*, in the press.

EXPERIMENTAL

Substrates.—Unlabelled 2-methylindole was from B.D.H. Ltd. Preparation and purification of the labelled materials have been described[1] and essentially involved either acid- or base-catalysed exchange of the 3-hydrogen with THO (The Radiochemical Centre, Amersham) or D_2O (Koch–Light Ltd). Specificity of the site of isotopic substitution was ascertained by a combined n.m.r. and i.r. spectral examination of the deuteriated compound. The 3-H n.m.r. resonance is displaced from those of other aromatic protons and for 2-methylindole in CCl_4 appears at τ 4·00 (1H, qu) relative to tetramethylsilane.[8] After exchange in D_2O this signal disappeared: no other change was observed apart from a decrease in the multiplicity of the 7-H band, consistent with deuteriation of both 3-H and 1-H (the latter gives a broad signal, detectable only in the integrated spectrum). I.r. spectra also showed deuterium substitution of both 1-H and 3-H: the most significant changes were disappearance of bands at 3400, 778, and 731 cm^{-1} with the appearance of new bands at 2500 and 736 cm^{-1}.

Dissolution of the deuteriated substance in distilled H_2O for a few minutes restored both the n.m.r. and i.r. signals assigned to 1-H. This showed that both labelling methods introduced deuterium at only the 1- and 3-positions and that the former could be removed before kinetic studies merely by dissolving the labelled substrate in H_2O. Since the tritiated substrate was prepared and used in an identical way, all the kinetic measurements refer to displacement of isotopic hydrogen from the 3-position only.

Reagents.—AnalaR acetic acid was used without further purification. Buffer solutions were prepared either by partial neutralization with B.D.H. standardised NaOH or by the addition of AnalaR sodium acetate. Ionic strengths were adjusted, where necessary, by the addition of AnalaR NaCl.

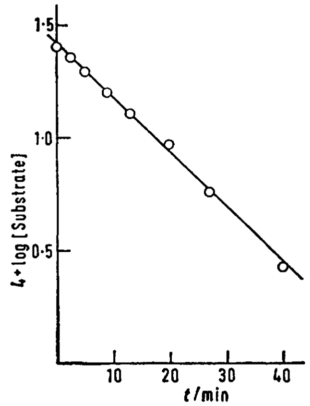
Deuterium oxide (Koch–Light, Ltd., 99·7% D) was purified for kinetic studies by repeated distillation from alkaline $KMnO_4$ to a conductivity $< 10^{-6}\ \Omega^{-1}$.

For the i.r. and u.v. assays, reagent and spectroscopic grades of 2,2,4-trimethylpentane were used, respectively.

Kinetics.—Protodetritiation rates were measured from the decrease in radioactivity of the substrate with time by use of a liquid scintillation method. Details were given in Part IV[1] for the base-catalysed reaction. The one difference here was that aliquot portions of the reaction solution were quenched in dilute alkali before extraction of the 2-methylindole with xylene. The same procedure was followed for the reactions in D_2O, with a general scaling down of quantities.

Protodedeuteriation rates were obtained from quantitative measurement of the i.r. absorption at 778 cm^{-1} corresponding to the C–H out-of-plane bending vibration for the 3-position.[9] The kinetic method was essentially the same as for the protodetritiation studies. Thus the reaction was initiated by the addition of the appropriate concentrated catalyst solution to an aqueous solution of 3-$^2H_1$-2-methylindole (50 mg) in a 100 ml volumetric flask immersed in a constant-temperature water-bath. At noted intervals, 10 ml aliquot portions were withdrawn with a pipette and run into separatory funnels containing 2,2,4-trimethylpentane (5 ml) plus sufficient dilute NaOH to neutralise the reaction mixture. After being shaken for 2 min the organic phase was allowed to separate (*ca.* 15 min). The organic layer containing the 2-methylindole was then removed in readiness for i.r. analysis. Each kinetic sample was checked for constancy of extraction by u.v. analysis ($\times 10$ dilution with 2,2,4-trimethylpentane, 1 mm cell at 264 nm).

The i.r. assay of the organic extract at 778 cm^{-1} in 3 mm AgCl cells was made with a Perkin-Elmer 621 spectrophotometer. Prior examination showed that the 778 cm^{-1} band was unaffected by neighbouring peaks including those of 3-$^2H_1$-2-methylindole. Concentrations of product in each sample were interpolated from a slightly curved calibration plot {[2-methylindole] against log 100/(% transmittance)} prepared from samples of known concentration. The calibration was checked frequently and, where feasible, calibration and kinetic spectra were taken concurrently.



First-order kinetic plot for protodedeuteriation of 3-$^2H_1$-2-methylindole in acetic acid buffer solution at 25 °C ([HOAc] = 10^{-3}M, [OAc$^-$] = 3 × 10^{-3}M, [Substrate] = 4·6 × 10^{-3}M)

Values of k_0^D [equation (1)] were obtained from the regular integrated first-order rate equation by a least-squares determination of the slope of log [3-$^2H_1$-2-methylindole] against time. The scatter of individual points was larger than for detritiation experiments, but was not excessive. Good linearity was apparent for those plots in excess of 90% reaction, as shown for a typical experiment in the Figure. The error in determining these rate coefficients was estimated as $\pm 6\%$, about twice as large as for the detritiation experiments.

RESULTS

Experimental first-order rate coefficients [equation (1)] for protodetritiation and protodedeuteriation in aqueous acetic acid buffers at 25 °C are listed in Tables 1 and 2 respectively. Because both 2-methylindole and its conjugate base undergo hydrogen exchange by S_E2 pathways,

$$\text{Rate} = k_0^L[\text{3-L}_1\text{-2-Methylindole}] \qquad (1)$$

k^L_0 is comprised of contributions from all the acid and base catalysts in the reaction solution. Under our experimental conditions, however, only H_3O^+ and HOAc are effective catalysts as contributions from H_2O, OH^-, and OAc^- are all negligible. This is evident from previous studies of 2-methylindole which show that the ratio of

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

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

second-order coefficients $k^{T}_{HOAc}/k^{T}_{OAc^-} \simeq 10^4$,[7,10] that $k^{T}_{OH^-} = 4{\cdot}54 \times 10^{-4}$ l mol^{-1} s^{-1},[1] and that $k^{T}_{H_2O} \times [H_2O] < 6 \times 10^{-8}$ s^{-1}.[11] Thus to a good approximation, k^{L}_{0} is related to the effective catalytic coefficients by equation (2). The data in Tables 1 and 2 refer to sets of experiments

$$k_0^{L} = k^{L}_{H_3O^+} \cdot [H_3O^+] + k^{L}_{HOAc} \cdot [HOAc] \qquad (2)$$

where either the pH (*i.e.*, fixed buffer ratio [HOAc] : [OAc$^-$]) or [HOAc] was constant. Thus $k^{L}_{H_3O^+}$ and k^{L}_{HOAc} could be evaluated from both the slopes of the appropriate plots of k_0^{L} against [HOAc] or [H$_3$O$^+$)] and their intercepts, which correspond to either $k^{L}_{H_3O^+} \cdot [H_3O^+]$ or $k^{L}_{HOAc} \cdot [HOAc]$. These coefficients are summarised in Table 3, with the intercept values in parentheses.

TABLE 1

Protodetritiation of 3-^{3}H$_1$-2-methylindole in HOAc buffers at 25 °C

10^3[HOAc]/M	10^3[NaOAc]/M [a]	10^6[H$_3$O$^+$]/M [b]	$10^4 k_0^{T}$/s^{-1}
1·0	5·0	5·58	2·81
5·0	25	5·58	5·80
10	50	5·58	9·35
15	75	5·58	12·7
20	100	5·58	15·7
1·0	1·0	27·9	11·4
1·0	2·0	14·0	6·47
1·0	3·0	9·29	4·38

[a] $\mu = 0{\cdot}1$ by addition of NaCl. [b] Calculated from $K_{HOAc} = 2{\cdot}79 \times 10^{-5}$ mol l^{-1}.

TABLE 2

Protodedeuteriation of 3-^{2}H$_1$-2-methylindole in HOAc buffers at 25 °C

10^3[HOAc]/M	10^3[NaOAc]/M [a]	10^6[H$_3$O$^+$]/M [b]	$10^4 k_0^{D}$/s^{-1}
1·0	10	2·79	3·31 (4·1) [c]
3·0	30	2·79	6·04
5·0	50	2·79	9·10
8·0	80	2·79	14·0
10	100	2·79	15·9 (16·1) [c]
1·0	1·0	27·9	25·5
1·0	2·0	14·0	13·2
1·0	3·0	9·29	9·09
1·0	5·0	5·58	6·55

[a] $\mu = 0{\cdot}1$ by addition of NaCl. [b] Calculated from $K_{HOAc} = 2{\cdot}79 \times 10^{-5}$ mol l^{-1}. [c] Duplicate runs.

TABLE 3

Second-order coefficients and isotopic rate ratios for 3-L$_1$-2-methylindole at 25 °C

Catalyst (HA)	k^{T}_{HA}/ l mol^{-1} s^{-1}	k^{D}_{HA}/ l mol^{-1} s^{-1}	k^{T}_{DA}/ l mol^{-1} s^{-1}	k_2^{H}/k_2^{D}	k_1^{HA}/k_1^{DA}
H$_3$O$^+$	40·8 (41·2) [a]	85·0 (78·9)	73·7 (58·6)	6·3 ∓ 1·0	2·59 ∓ 0·5
HOAc	0·069 (0·057)	0·144 (0·150)	0·044 (0·044)	6·3 ∓ 1·0	7·3 ∓ 1·4

[a] Values in parentheses from intercepts (see text).

Solvent isotope effects were also measured from studies with 3-^{3}H$_1$-2-methylindole in acetic acid buffers made up in D$_2$O. The deuterium atom fraction of these solutions >0·99 and [D$_3$O$^+$] was calculated on the basis that $(pK_{DOAc})_{D_2O} - (pK_{HOAc})_{H_2O} = 0{\cdot}5145$.[12] Experimental data for these reactions, where either [DOAc] or pD is constant, are in Table 4. Second-order coefficients $k^{T}_{D_3O^+}$ and k_{DOAc} were derived as for the H$_2$O reactions and are included in Table 3.

TABLE 4

Deuteriodetritiation of 3-^{3}H$_1$-2-methylindole in DOAc buffers at 25 °C

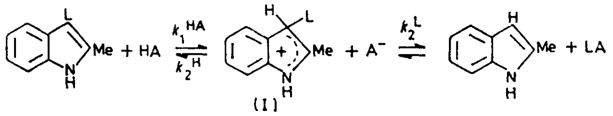
10^3[DOAc]/M	10^3[NaOAc]/M [a]	10^7[D$_3$O$^+$]/M [b]	$10^4 k_0^{T}$/s^{-1}
1·0	10	8·53	0·92
4·0	40	8·53	2·15
7·0	70	8·53	3·47
10	100	8·53	4·85
10	10	85·3	10·6
10	20	42·6	7·65
10	50	17·1	5·70

[a] $\mu = 0{\cdot}1$ by addition of NaCl. [b] Calculated from $K_{DOAc} = 8{\cdot}53 \times 10^{-6}$ mol l^{-1}.

DISCUSSION

Agreement between second-order coefficients derived from slopes or intercepts is reasonable (Table 3), justifying the assumption that an insignificant amount of hydrogen exchange comes from catalysis by H$_2$O and any basic species. Also coefficients for the H$_3$O$^+$ and HOAc-catalysed detritiation agree within a few per cent. with values from another laboratory ($k^{T}_{H_3O^+} = 44$ l mol^{-1} s^{-1}; $k^{T}_{HOAc} = 0{\cdot}069$ l mol^{-1} s^{-1}.[7] In calculating isotopic rate ratios, however, we have utilised coefficients from the slopes only of this coherent set of measurements.

Table 3 shows that deuterium is displaced more rapidly from the substrate than tritium by both H$_3$O$^+$ and HOAc. Also there are substantial solvent isotope effects with a 36% reduction in rate by DOAc and a 91% increase by D$_3$O$^+$.



SCHEME A–S_E2 Exchange mechanism for 3-L$_1$-2-methylindole in H$_2$O

An A–S_E2 exchange mechanism (Scheme) involves reaction *via* the relatively stable conjugate acid (I), where HA represents the acid catalyst (in this case H$_3$O$^+$ or HOAc or their deuteriated counterparts). Although this process must be totally reversible, under the kinetic conditions the reverse reaction to k_2^{L} is effectively zero because the concentration of the isotopic species (LA) is never appreciable. Breakdown of intermediate (I) to products (k_2^{L}) is rate-limiting, but breakdown to reactants (k_2^{H}) is little faster than the normal primary hydrogen isotope effect (*i.e.*, a factor of *ca.* 16 for 3-^{3}H$_1$-methylindole).[13] By implication, the formation of conjugate acid (k_1^{HA}) must also be relatively slow.

The kinetic dependence of each step in the Scheme on the experimental second-order coefficient (k^{L}_{HA}) for

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[10] Part III, B. C. Challis and F. A. Long, *J. Amer. Chem. Soc.*, in the press.

[11] Part I, B. C. Challis and F. A. Long, *J. Amer. Chem. Soc.*, 1963, **85**, 2524.

[12] R. Gary, R. G. Bates, and R. A. Robinson, *J. Phys. Chem.*, 1965, **69**, 2750; V. Gold and B. M. Lowe, *J. Chem. Soc.* (*A*), 1968, 1923.

[13] R. P. Bell, 'The Proton in Chemistry,' Methuen, London, 1959, p. 202.

catalysis by HA is derived readily from steady-state kinetic theory which leads to equation (3). It is obvious that coefficients for the individual steps cannot

$$k^{\mathrm{L}}_{\mathrm{HA}} = k_1^{\mathrm{HA}}/(1 + k_2^{\mathrm{H}}/k_2^{\mathrm{L}}) \qquad (3)$$

be deduced directly from $k^{\mathrm{L}}_{\mathrm{HA}}$, but isotopic rate ratios are accessible in the way described by Kresge and Chiang[14] *via* solution of simultaneous forms of equation (3). The relevant expressions are given as equation (4) for

$$k^{\mathrm{T}}_{\mathrm{HA}} = \frac{k_1^{\mathrm{HA}}}{1 + (k_2^{\mathrm{H}}/k_2^{\mathrm{D}})^{1\cdot442}} \qquad (4)$$

$$k^{\mathrm{D}}_{\mathrm{HA}} = k_1^{\mathrm{HA}}/(1 + k_2^{\mathrm{H}}/k_2^{\mathrm{D}}) \qquad (5)$$

$$k^{\mathrm{T}}_{\mathrm{DA}} = \frac{k_1^{\mathrm{DA}}}{1 + (k_2^{\mathrm{H}}/k_2^{\mathrm{D}})^{0\cdot442}} \qquad (6)$$

protodetritiation in H_2O, as equation (5) for protodedeuteriation in H_2O, and as equation (6) for deuteriodetritiation in D_2O.

Values of $k_1^{\mathrm{HA}}/k_1^{\mathrm{DA}}$ and $k_2^{\mathrm{H}}/k_2^{\mathrm{D}}$ derived in this way for both acetic acid and lyonium ion catalysis are also given in Table 3. Before we discuss their magnitudes, it should be noted that factors other than differences of bond fission rates (*i.e.*, primary isotope effects) may contribute to these rate ratios on account of approximations made in deriving equations (4)—(6). In particular, no account has been taken of secondary isotope effects arising from change of solvent (H_2O *versus* D_2O) and leaving atom (tritium *versus* deuterium). Kresge and Chiang[4] have shown from studies of trimethoxybenzene that allowance for these factors increases both $k_2^{\mathrm{H}}/k_2^{\mathrm{D}}$ and $k_1^{\mathrm{HA}}/k_1^{\mathrm{DA}}$; thus values cited in Table 3 should be regarded as minimum primary isotope effects.

Although $k_1^{\mathrm{HA}}/k_1^{\mathrm{DA}}$ and $k_2^{\mathrm{H}}/k_2^{\mathrm{D}}$ refer to the forward and reverse steps of the same chemical process (conversion of 2-methylindole into its conjugate acid), they should not be of equal magnitude since they refer to zero-point energy differences associated with O–H and C–H bonds, respectively. The difference for the acetic acid-catalysed reaction (Table 3) is very similar to that reported for other A–$S_{\mathrm{E}}2$ exchange reactions.[3] The low figure for $k_1^{\mathrm{HA}}/k_1^{\mathrm{DA}}$ for lyonium ion catalysis is an established phenomenon[15] arising from an inverse secondary isotope effect owing to water molecules solvating the proton: a maximum of *ca.* 3·6 has been predicted for this ratio.[16]

The Brønsted exponent for general-acid catalysed protodetritiation of 3-$^3H_1$-2-methylindole was reported in Part II as $\alpha = 0{\cdot}46$.[7] Although rigorous quantitative relationships seem unlikely, it has been widely suggested,[17] and shown experimentally by Long[3] and by Kresge[4] and their colleagues for some aromatic hydrogen exchange reactions, that median Brønsted exponents imply a symmetrical transition state for proton transfer and, in turn, substantial primary isotope effects. The results for 2-methylindole are not out of line with these conclusions. Isotopic rate ratios in Table 3 are from 70 to 90% of those predicted on the basis of simple zero-point energy differences[13] and similar to those for azulenes[3] and trimethoxybenzenes[4] for which α is also close to 0·5. They are entirely consistent with the assumption of an A–$S_{\mathrm{E}}2$ exchange mechanism.

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