Heteroaromatic Hydrogen Exchange Reactions. Part VII.[1] Isotope Effects for the Base-catalysed Exchange of 3-$^2H_1$- and 3-$^3H_1$-Indoles in Aqueous Sodium Hydroxide

By **B. C. Challis,*** Department of Organic Chemistry, Imperial College, London S.W.7
E. M. Millar, Chemistry Department, St. Salvators College, St. Andrews, Fife

Rates of protodedeuteriation in aqueous NaOH at 25 °C are reported for indole and 2-methylindole labelled at the 3-position, together with rates of deuteriodetritiation of the 2-methyl compound in NaOD. Calculation of various isotopic rate ratios from this and previous data for the corresponding protodetritiation reaction show unequivocally the incidence of an S_E2 mechanism involving the indole anion and water. Critical examination shows that the isotope effects for these reactions are relatively insensitive to the symmetry of the transition state for the proton-transfer process.

PREVIOUS studies of general-base catalysis[2] and of protodetritiation in concentrated NaOH[3] point to an S_E2 mechanism for the base-catalysed isotopic hydrogen exchange of indole compounds involving reaction between an acid catalyst and the indole anion. One other characteristic of this pathway is that proton transfer between the catalyst and substrate is slow. Thus the observation of substantial hydrogen isotope effects would be powerful confirmation of the S_E2 mechanism.

Acid-catalysed isotopic hydrogen exchange of many aromatic substrates,[4] including indole,[5] proceeds by an analogous A–S_E2 pathway involving the neutral substrate. As discussed in Part VI,[1] these reactions have attracted considerable attention in connection with the kinetic features of proton-transfer phenomena, particularly with respect to the structure of the transition state. It is apparent that results for azulenes,[6] which have been regarded as good support for theoretical predictions[7] that primary isotope effects are strongly dependent on the degree of proton transfer, are at variance with those for substituted indoles. Further, examination of all the results for A–S_E2 hydrogen exchange reactions suggest that k_H/k_D ratios are relatively insensitive to ΔpK ($= pK_{substrate} - pK_{catalyst}$), which has been suggested[8] as an index of transition-state symmetry. It is not clear, however, whether this arises from inadequacies of the ΔpK index or from other factors. In this context, isotope effects associated with the hydroxide ion-catalysed hydrogen exchange of indoles reported in this paper should be illuminating, as several factors suggest that their transition states are highly unsymmetrical.

EXPERIMENTAL

All the substrates were purchased as unlabelled compounds; indole and 2-methylindole from B.D.H. and 5-cyanoindole from Aldrich. Substitution with isotopic hydrogen was effected by acid-catalysed exchange with either THO (The Radiochemical Centre) or D_2O (Koch–Light). Details of the labelling procedure and purity checks have been given.[3]

Reaction solutions were usually prepared from B.D.H. 'carbonate-free' standardised NaOH. For the solvent isotope effect studies, however, AnalaR NaOH was dissolved in 99·7% D_2O (Koch–Light) which had been repeatedly distilled from alkaline $KMnO_4$ to a conductivity $<10^{-6}$ ohm^{-1}. The deuterium atom fraction in these reaction solutions was in excess of 0·99. The alkalinity of the reaction solutions was checked by titration against standardised HCl with Methyl Red as indicator.

Protodetritiation rates were measured from the decrease of radioactivity of the substrate with time by use of a liquid scintillation counting assay. Protodedeuteriation was followed independently from i.r. spectral changes of the substrate. Details are in earlier papers.[1,3,5]

RESULTS

As in previous studies of these reactions,[2,3] the rate of isotopic hydrogen exchange in dilute aqueous NaOH has an accurate first-order dependence on substrate concentration in excess of 90% reaction. Experimental rate coefficients [equation (1)] measured for protodetritiation of 3-$^3H_1$-2-methylindole in D_2O and protodedeuteriation of 3-$^2H_1$-indole and its 2-methyl derivative in H_2O, all at 25 °C, are in Table 1. In every case, k_0 increases regularly with [NaOH] and a first-order dependence on this term also is evident. Mean values of the second-order coefficient $k^L_{OH^-}$ [equation (2)] are in Table 2 for the reactions investigated here together with those reported earlier[3] for the protodetritiation of 3-$^3H_1$-indole and its 2-methyl derivative in dilute aqueous NaOH.

$$\text{Rate} = k_0[3\text{-}L_1\text{-InH}]\,\dagger \qquad (1)$$

$$\text{Rate} = k^L_{OH^-}[3\text{-}L_1\text{-InH}][\text{NaOH}] \qquad (2)$$

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† The symbol L refers to tritium or deuterium as appropriate. The neutral form of the indole is denoted by InH, and its conjugate base by In$^-$.

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

[2] Part III, B. C. Challis and F. A. Long, submitted to *J. Amer. Chem. Soc.*

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

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

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

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[7] F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265; R. P. Bell, *Discuss. Faraday Soc.*, 1965, **39**, 16; R. A. More O'Ferrall and J. Kouba, *J. Chem. Soc.* (*B*), 1967, 985.

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DISCUSSION

Our previous investigations of the base-catalysed process with these compounds suggests that hydrogen exchange proceeds *via* the conjugate base. Salient factors in this deduction were the relative stability of *N*-methylated derivatives[9] and the incursion of a limiting rate in concentrated NaOH, where complete conversion of the substrate into its conjugate base would be expected.[4]

TABLE 1

Experimental first-order rate coefficients (k_0/s^{-1}) for hydrogen exchange of 3-L_1-indoles in aqueous sodium hydroxide at 25 °C

10^2[NaOH]([NaOD])/M	10^2[NaCl]/M	10^5k_0
3-$^2H_1$-2-Methylindole in NaOH		
1·00	9·00	0·88
3·00	7·00	2·90
5·00	5·00	4·33
6·00	4·00	6·00
8·00	2·00	7·30
10·00		9·05 (9·05) [a]
3-$^3H_1$-2-Methylindole in NaOD(D_2O)		
0·94	9·50	0·34
3·90	6·54	1·32
6·06	4·38	2·15
10·44		3·78
3-$^2H_1$-Indole in NaOH		
40·0		1·15
80·0		2·47
100		3·21 (3·32) [a]

[a] Duplicate kinetic runs.

TABLE 2

Mean second-order coefficients (k/l mol^{-1} s^{-1}) [equation (2)] for hydrogen exchange of 3-L_1-indoles in aqueous sodium hydroxide at 25 °C

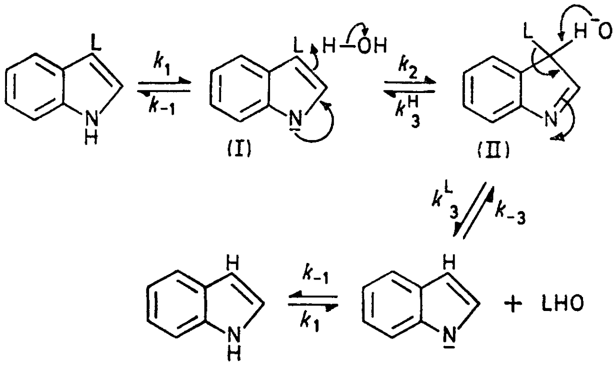
Substrate	$10^6k^T{}_{OH^-}$	$10^6k^D{}_{OH^-}$	$10^6k^T{}_{OD^-}$
3-L_1-2-Methylindole	454 ± 10 [a]	900 ± 30	354 ± 8
3-L_1-Indole	17·8 ± 0·2 [a]	31·1 ± 1·6	

[a] From ref. 3.

The substrates are such weak acids (pK_a >15)[10] that under the mildly alkaline conditions used to examine the isotope effects, the conjugate base is at low, steady-state concentration. Also the alkalinity of these solutions is adequately expressed by the stoicheiometric [NaOH], as activity-coefficient corrections are too small to require the use of H_- acidity function approximations. These considerations vindicate equation (2).

The experimental results indicate a significant isotope effect, with deuterium displacement occurring about twice as rapidly as that of tritium for both compounds. Experiments with 3-$^3H_1$-2-methylindole show the incidence of a solvent isotope effect, too, with a rate reduction of *ca.* 25% in D_2O. For a reaction involving the conjugate base and subject to general base catalysis, these observations are consistent only with an S_E2 mechanism as described by the Scheme.

By themselves, these experimental observations give no definitive information on the rate-limiting step: they are equally consistent with either a product or a kinetic isotope effect for the S_E2 mechanism. However, evidence in Part IV[3] shows the initial ionization to form anion (I) is rapid and reversible, and the present results, notably that indole reacts 17 times more slowly than 2-methylindole despite their similar acid strength, reinforce this conclusion. By implication, then, subsequent steps involving formation and decomposition of the indolenine intermediate (II) are rate-limiting (*i.e.*, k_2 and $k^L{}_3$), and the observed isotope effects are therefore of the kinetic kind. Both k_2 and $k^L{}_3$ are, of course, reversible, but $k^L{}_3$ can be discounted from the kinetic treatment because the substrate concentration is always very low (*ca.* 10^{-4}M). The reverse of k_2 differs from $k^L{}_3$ only in respect of the leaving atom and is therefore defined as $k^H{}_3$. An important point is that k_2 cannot be much larger than $k^L{}_3$ because no build-up of 3*H*-indole tautomer (II) concentration can be detected during the reaction. Thus the base-catalysed pathway is directly analogous to the acid-catalysed (*A*–S_E2) one, differing in respect of an anionic rather than neutral reactant only.



SCHEME S_E2 Mechanism for the base-catalysed hydrogen exchange of 3-L_1indoles

The kinetic dependence of each step in the Scheme on the experimental rate is derived readily from the application of steady-state kinetic theory [equations (3) and (4)] with $K_E = [In^-][H_2O]/[InH][OH^-]$. By

$$\text{Rate} = \frac{k_2}{1 + k^H{}_3/k^L{}_3}\{[3\text{-}L_1\text{-}In^-][H_2O]\} \qquad (3)$$

$$= \frac{K_E \,.\, k_2}{1 + k^H{}_3/k^L{}_3}\{[3\text{-}L_1\text{-}InH][OH^-]\} \qquad (4)$$

comparison with equation (2), the relationship to the experimental second-order coefficient ($k^L{}_{OH^-}$) is obtained directly [equation (5)]. Apart from the inclusion of the equilibrium constant (K_E), equation (5) is identical with

$$k^L{}_{OH^-} = \frac{K_E \,.\, k_2}{1 + k^H{}_3/k^L{}_3} \qquad (5)$$

that for the acid-catalysed (*A*–S_E2) hydrogen exchange of indoles.[1]

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

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

As in the preceding paper, rate coefficients for the individual steps (k_2, k^{L}_3, and k^{H}_3) cannot be deduced directly from $k^{L}_{OH^-}$, but isotopic rate ratios can be obtained by the method of Kresge and Chiang [11] involving the solution of simultaneous forms of equation (5). The relevant expressions for the present case are given as equations (6)—(8) and both the kinetic isotope

For protodetritiation in H_2O:

$$k^{T}_{OH^-} = (K_E)_{H_2O}\,\frac{k^{H_2O}_2}{1 + (k^{H}_3/k^{D}_3)^{1{\cdot}442}} \qquad (6)$$

For protodeuteriation in H_2O:

$$k^{D}_{OH^-} = (K_E)_{H_2O}\,\frac{k^{H_2O}_2}{1 + k^{H}_3/k^{D}_3} \qquad (7)$$

For deuteriodetritiation in D_2O:

$$k^{T}_{OD^-} = (K_E)_{D_2O}\,\frac{k^{D_2O}_2}{1 + (k^{H}_3/k^{D}_3)^{0{\cdot}442}} \qquad (8)$$

effect (k^{H}_3/k^{D}_3) and the solvent isotope effect $[k^{H_2O}_2 \,.\, (K_E)_{H_2O}]/[k^{D_2O}_2 \,.\, (K_E)_{D_2O}]$ can be obtained from them. Substitution of the appropriate experimental results from Table 3 leads to the values of 5·7 ± 0·6 and 4·4 ± 0·5 for k^{H}_3/k^{D}_3 for 2-methylindole and indole respectively, and 5·6 ± 0·6 for the solvent isotope effect for 2-methylindole.

The major contributor to any of these ratios is the primary isotope effect associated with rate-limiting hydrogen bond fission and, because of approximations made in deriving equations (6)—(8), they tend to underestimate rather than overestimate this contribution. In particular, no account is taken of secondary isotope effects arising from changes of either solvent (H_2O *versus* D_2O) or isotopic label in the substrate (tritium *versus* deuterium). From related studies of acid-catalysed (A–S_E2) hydrogen exchange of trimethoxybenzene,[11a] it is known that allowance for these factors increases both k^{H}_3/k^{D}_3 and $k^{H_2O}_2/k^{D_2O}_2$ ratios. Any correction should be in the same direction for the S_E2 reactions, so the cited values of these ratios may be regarded as minimum primary isotope effects.

Also, the results for 2-methylindole seem to be reasonably self-consistent. Any medium effects on the dissociation-constant ratio should be quite small [*i.e.*, $(K_E)_{H_2O} = (K_E)_{D_2O}$], because the acid strengths of H_2O (pK_a = 15·75) and 2-methylindole (pK_a = 16·45) [3] are very similar. Thus, to a good approximation, $k^{H_2O}_2/k^{D_2O}_2 = 5{\cdot}6 \mp 1{\cdot}0$. This ratio comprises a primary isotope effect for O–H bond fission plus a secondary effect arising from changes in solvating water molecules as a proton is transferred from water to the substrate. The latter can be calculated by Bunton and Shiner's [12] treatment as an inverse factor of between 0·87 and 0·60, depending, respectively, on whether the proton is completely or half-transferred to the substrate. Thus the primary isotope effect for O–H bond fission must lie in the range 6·44 (5·6/0·87) to 9·33 (5·6/0·60). This represents from 56 to 80% of the predicted maximum ratio of 11·6 based on a simple consideration of zero-point energy differences for an O–H stretching vibration of 3400 cm^{-1} assigned to the bonded water molecule.[13] On the basis of a C–H stretching vibration of 2900 cm^{-1} for a methylene group, the kinetic isotope ratio for 2-methylindole (k^{H}_3/k^{D}_3 = 5·7) corresponds to 73% of the equivalent maximum value of 7·8.[11b] Thus the extents of proton transfer in the transition state evaluated from each isotopic ratio do not conflict, and this justifies the assumption of an S_E2 exchange mechanism.

These results seem to have an important bearing on recent investigations of the relationship between the symmetry of the transition state for proton-transfer reactions and experimentally accessible data such as primary hydrogen isotope effects and exponents for Brønsted acid–base catalysis. It is evident from the preceding paper that several significant correlations have been reported for proton abstraction from pseudo-acid species and for aromatic (A–S_E2) hydrogen exchange reactions. For the acid-catalysed (A–S_E2) hydrogen exchange of indoles, however, kinetic isotope effects are substantial (k_H/k_D = 4·5—6·7) but relatively insensitive to either substrate or catalyst reactivity. Further, the data for A–S_E2 hydrogen exchange of azulenes [6] and trimethoxybenzenes [11] are not wholly inconsistent with the indole results. The question arises whether this reflects a relatively constant transition state with respect to proton transfer throughout these compounds or whether the k_H/k_D ratio is a poor index of any change.

The Brønsted exponent for general-acid catalysed hydrogen exchange of the 3-$^{3}H_1$-2-methylindole anion (*i.e.*, the S_E2 reaction) is large (α = 0·86).[2] Although the exact physical significance of α exponents has been repeatedly questioned,[14] its magnitude here suggests a transition state in which the proton is largely transferred to the substrate, which is implicit with the known instability of the 3*H*-indole tautomer (II), the probable intermediate on the reaction path. Thus the appreciable kinetic isotope effect reported for hydroxide ion catalysis (k^{H}_3/k^{D}_3 = 5·7), which is not very different from those for the A–S_E2 reaction,[1] does not seem to reflect this asymmetry. Relative to 2-methylindole, k^{H}_3/k^{D}_3 for S_E2 exchange of indole is 20% less, and the difference in their reactivity is a factor of *ca.* 17. This change might be regarded as tentative evidence that isotope effects for the S_E2 reaction vary significantly with substrate reactivity. However, preliminary results for 5-cyanoindole, 20 times less reactive than indole,[3] clearly suggest otherwise: in 0·1M-NaOH, at 25 °C, second-order coefficients are $k^{T}_{OH^-} = 12{\cdot}5 \times 10^{-6}$ l mol^{-1} s^{-1} [3] and $k^{D}_{OH^-} = 25{\cdot}8 \times 10^{-6}$ l mol^{-1} s^{-1}; thus the kinetic isotope ratio $k^{H}_3/k^{D}_3 = 5{\cdot}4 \mp 1{\cdot}0$. Since $k^{T}_{OAc^-} = 8{\cdot}7 \times 10^{-7}$

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l mol^{-1} s^{-1},[1] the approximate Brønsted exponent for this reaction is $\alpha = 0{\cdot}9$.

Thus kinetic isotope ratios (and possibly primary isotope effects) for at least some aromatic hydrogen exchanges seem to be insensitive to the extent of transition-state proton transfer, measured either by the free-energy change (ΔpK) of the reaction (as in the preceding paper) or by other kinetic parameters. This observation is in line with recent deductions by Bell and his colleagues [15] that varying primary isotope effects, widely reported for proton abstraction from aliphatic pseudo-acids, arise from differences of proton tunnelling rather than transition-state symmetry. It is conceivable that proton donation and removal are concerted for aromatic hydrogen exchange, which might make secondary hydrogen isotope effects strongly dependent on catalyst and substrate structure and allow them to compensate for variations of the primary isotope effect. At present, however, this explanation is not substantiated by any experimental observation.[1,16] As far as other aromatic substitutions are concerned, substantial evidence that the size of the primary hydrogen isotope effect is strongly dependent on catalyst reactivity is found only for diazo-coupling,[17] and these reactions are known to be sensitive to steric interaction [18] which often favours the incidence of proton tunnelling. We therefore conclude that the magnitude of kinetic hydrogen isotope effects for aromatic hydrogen exchange give no reliable information about the transition state, and, in view of Bordwell and Boyle's [19] similar findings for proton abstraction from 1-arylnitroethanes, this conclusion may have wider implication.

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