Heteroaromatic Hydrogen Exchange Reactions. Part 9.[1] Acid Catalysed Decarboxylation of Indole-3-carboxylic Acids

By **Brian C. Challis** * and **Henry S. Rzepa**, Department of Chemistry, Imperial College, London SW7 2AZ

Rates of acid catalysed decarboxylation in both H_2O and D_2O at 25° are reported for indole-3-carboxylic acid and its 2-methyl and 5-chloro-derivatives, and for indole-3-carboxylic acid in aqueous pyridine buffers at 60°. The experimental data are shown to fit well with the kinetic expression (Rate = $\{a + b[L_3O^+]/(1 + c[L_3O^+])\}$ [Substrate]) obtained for the decarboxylation of other aromatic and heteroaromatic acids, consistent with an A–S_E2 mechanism involving a zwitterionic intermediate. Evaluation of the parameters b and c gives solvent deuterium isotope effects for reaction *via* both the neutral substrate and the carboxylate anion, from which primary isotope effects for proton transfer from the solvent to the substrate can be assessed. These primary isotope effects are remarkably similar (2.23—2.72) for all three indole-3-carboxylic acids. Further, comparison with decarboxylation data for azulene-1-carboxylic acid, and with other results for the protonation of indole compounds, shows there is no systematic variation in the solvent isotope effect for proton transfer (all of which lie in the limited range 2.23—2.87) over a reactivity span of *ca.* 10^6. This implies that primary isotope effects are little influenced by substrate reactivity and, *inter alia*, by the symmetry of the transition state for proton transfer.

STUDIES of various compounds have established that protiodecarboxylation of aromatic and heteroaromatic acids usually proceeds by an A–S_E2 mechanism.[2] From the most critical studies carried out by both Long [2e,f] and by Dunn [2h] and their colleagues with azulenium and pyrrole substrates, respectively, it is also clear that proton transfer from the solvent to the aromatic nucleus can be rate limiting under certain conditions. Both primary hydrogen isotope effects and Brønsted acid catalysis may therefore be expected, and, indeed, their incidence has been demonstrated in a number of examples.[2a,b,d,e,g,h]

Previously we determined kinetic isotope effects for hydrogen exchange of indole compounds [3] and, contrary to most findings for innumerable other proton transfer reactions,[4] their magnitudes were substantially independent of the substrate reactivity.[5] These results therefore question recent assertions [6] that the magnitude of the primary isotope effect is an index of transition state symmetry for proton transfer processes. By and large, this hypothesis continues to be widely accepted, although another explanation dependent on the incidence of proton tunnelling has also been advanced to account for variable primary isotope effects.[7] We have considered [3] that isotopic rate ratios for aromatic hydrogen exchange (such as with indole) may be exceptional because of the symmetrical character of the reaction. Thus two hydrogen atoms are involved in the transition state and it is conceivable that constant kinetic isotope effects may arise either because hydrogen exchange is concerted or from abnormally large secondary hydrogen isotope effects mitigating the variation of the primary effect with subsubstrate reactivity. Neither of these explanations, however, is well supported by the meagre experimental evidence available: for example, Kresge's [8] careful analysis of secondary isotope effects for hydrogen exchange of trimethoxybenzene shows them to be rather small, and there is good evidence that hydrogen exchange of azulene is not concerted.[9] Thus for aromatic hydrogen exchange reactions, at least, the magnitude of the primary isotope effect does not seem to reflect the transition state symmetry.

To test this conclusion further, we have therefore examined hydrogen isotope effects for the protiodecarboxylation of indole-3-carboxylic acids. From the isotopic rate ratio standpoint, these reactions are simpler than hydrogen exchange insofar as only a single hydrogen transfer is involved, and, further, substrate reactivity can be conveniently varied by substituents remote from the reactive site. These compounds are known to decarboxylate qualitatively in acidic solutions [10] and it seems likely that an A–S_E2 mechanism will apply as for other aromatic and heteroaromatic acids.

RESULTS AND DISCUSSION

Good first-order plots up to 98% decarboxylation (see Experimental section) were obtained for all three indole-3-carboxylic acids examined and these reactions must therefore follow equation (1). The variation of k_0 with solvent acidity in both H_2O and D_2O was of prime

$$\text{Rate} = k_0[\text{Substrate}] \qquad (1)$$

interest, and decarboxylation rates were therefore

---

[1] Part 8, B. C. Challis and H. S. Rzepa, *J.C.S. Perkin II*, 1975, 1822.

[2] (*a*) A. Willi, C. M. Won, and P. Vilk, *J. Phys. Chem.*, 1968, **72**, 3142; (*b*) A. Willi, C. M. Won, and M. H. Cho, *Helv. Chim. Acta*, 1970, **53**, 663; (*c*) M. Zielinski, *Roczniki Chem.*, 1968, **42**, 1725; (*d*) D. S. Noyce, L. M. Gartler, F. B. Kirby, and M. D. Schiavelli, *J. Amer. Chem. Soc.*, 1967, **89**, 6944; (*e*) J. L. Longridge and F. A. Long, *J. Amer. Chem. Soc.*, 1967, **89**, 1292; 1968, **90**, 3092; (*f*) F. A. Long and H. H. Huang, *J. Amer. Chem. Soc.*, 1969, **91**, 2872; (*g*) G. E. Dunn and S. K. Dyal, *Canad. J. Chem.*, 1970, **48**, 3349; (*h*) G. E. Dunn and K. J. G. Lee, *ibid.*, 1971, **49**, 1032; (*i*) G. E. Dunn, K. J. G. Lee, and H. Thimm, *ibid.*, 1972, **50**, 3017.

[3] B. C. Challis and E. M. Millar, *J.C.S. Perkin II*, 1972, 1116, 1618, 1625.

[4] For examples and summaries see M. Wolfsberg, *Ann. Rev. Phys. Chem.*, 1969, 449; D. J. Barnes and R. P. Bell, *Proc. Roy. Soc.*, 1970, *A*, 318, 421; R. P. Bell and B. G. Cox, *J. Chem. Soc.* (*B*), 1971, 783; D. J. McLennan and R. J. Wong, *J.C.S. Perkin II*, 1974, 526.

[5] Constant isotope effects for substrates of varying reactivity have been reported by F. G. Bordwell and W. J. Boyle, *J. Amer. Chem. Soc.*. 1971, **93**, 511 and by D. S. Kemp and M. L. Casey, *J. Amer. Chem. Soc.*, 1973, **95**, 6670.

[6] F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265; R. A. More O'Ferrall and J. Kouba, *J. Chem. Soc.* (*B*), 1967, 985.

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

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

[9] B. C. Challis and F. A. Long, *Discuss. Faraday Soc.*, 1965, **39**, 67.

[10] G. R. Allen, C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, 1966, **88**, 2536; J. C. Powers, *Tetrahedron Letters*, 1965, 655.

measured in *ca.* 10^{-4}—1M-HCl (or DCl) at an ionic strength (μ) = 1 maintained by the addition of NaCl. These results are summarised in Figure 1—3 for indole-3-carboxylic acid, and its 2-methyl and 5-chloro-derivatives, respectively, where the experimental data (circles) are compared with values of k_o calculated in accordance with equation (2) and plotted as solid lines in the Figures. Both Longridge and Long (for azulene-1-carboxylic acid) [2e] and Dunn and Lee [2h] (for pyrrolecarboxylic acids) found previously that the acidity dependence of k_o in moderately dilute acids followed equation (2), and a similar relationship was anticipated for the indole

$$k_o = (a + b[L_3O^+])/(1 + c[L_3O^+]) \; * \qquad (2)$$

substrates. This was tested by non-linear, least squares regression analysis (see Experimental section) of the experimental data. In every case, an excellent fit to equation (2) was observed (Figures 1—3) and confirmed statistically by the *F* test.[11] Values obtained for the parameters *a*—*c* by this procedure are given in Table 1. This suggests that the indole-3-carboxylic acids follow a similar decarboxylation mechanism (Scheme 1) to that proposed for azulenium [2e] and pyrrole [2h] substrates. An important feature of this mechanism is that CO_2 is supposed to be lost only from the zwitterion (1), which may form *via* two alternative pathways involving prototropic equilibria as shown. The conjugate acid species (2) is believed to be stable, and this accounts for the fall-off in decarboxylation rates observed at high solvent acidities.

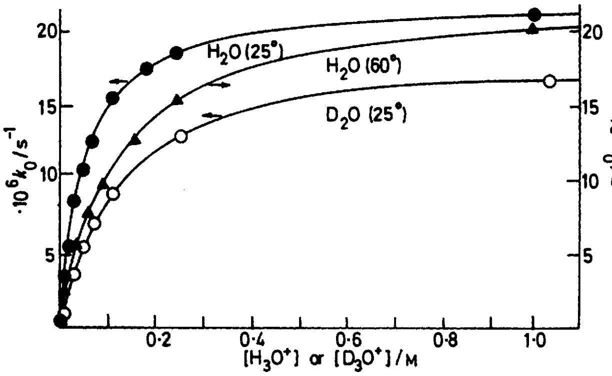


FIGURE 1 Decarboxylation of indole-3-carboxylic acid in H_2O at 25 and 60 °C and in D_2O at 25 °C

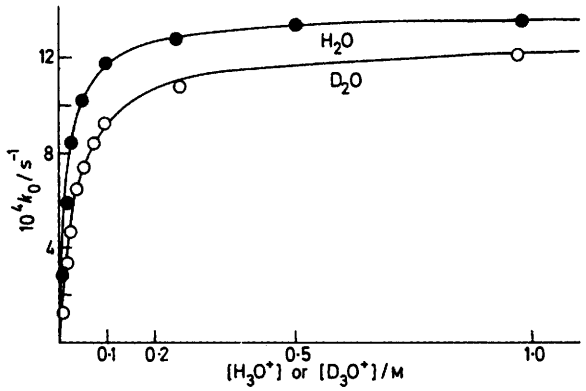


FIGURE 2 Decarboxylation of 2-methylindole-3-carboxylic acid in H_2O and D_2O at 25 °C

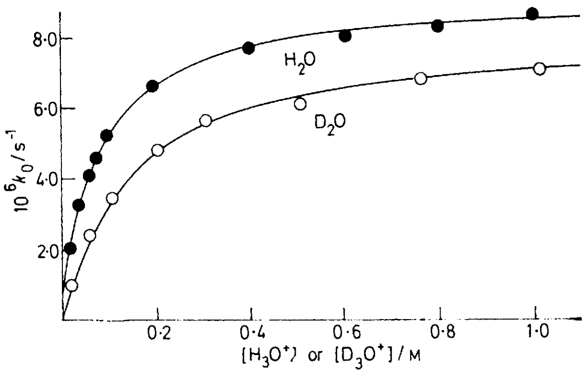
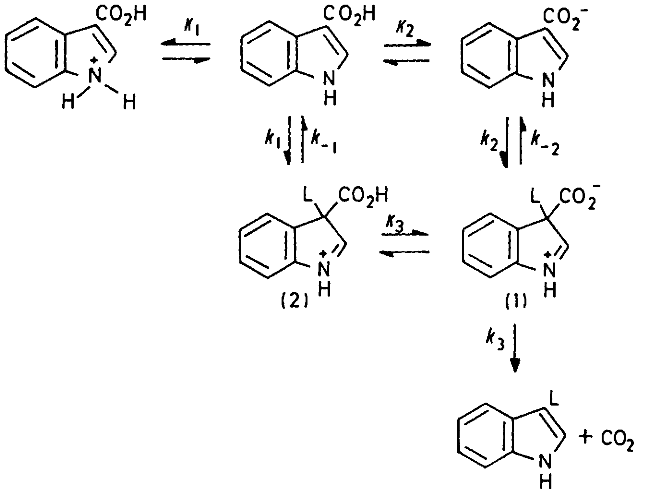


FIGURE 3 Decarboxylation of 5-chloroindole-3-carboxylic acid in H_2O and D_2O at 25 °C



SCHEME 1 *A*–S_E2 Decarboxylation mechanism for indole-3-carboxylic acids

Application of steady state approximations to the kinetics for Scheme 1 leads to a complex expression [equation (3)] for the observed rate.[2g,h] Under certain constraints, however, equation (3) simplifies considerably. Thus, the low basicity of indole nitrogen ($pK_1 \leqslant -6$),[12] but relatively high basicity of carboxylate oxygen (pK_2 *ca.* 5.5—6.0) [13] imply that both $[L_3O^+]/K_1 \ll 1$ and $K_2/[L_2O^+] \ll 1$ for the range of acidities examined

$$k_o = \frac{K_2k_2 + k_1[L_3O^+]}{1 + [L_3O^+]/K_1 + K_2/[L_3O^+]} \cdot \frac{K_3k_3}{K_3(k_3 + k_{-2}) + k_{-1}[L_3O^+]} \qquad (3)$$

here. Further, the absence of ^{13}C isotope effects noted for decarboxylation at low acidities [2h] suggests that k_3

---

* Throughout the text, L refers to either hydrogen or deuterium where appropriate.

[11] W. E. Wentworth, *J. Chem. Educ.*, 1965, **42**, 65, 162.

[12] H. J. Chen, L. E. Hakka, R. L. Hinman, A. J. Kresge, and E. B. Whipple, *J. Amer. Chem. Soc.*, 1971, **93**, 5102.

[13] M. S. Melzer, *J. Org. Chem.*, 1962, **27**, 496.

$\gg k_{-2}$. On implementing these approximations, equation (2) is obtained, where $a = K_2k_2$, $b = k_1$, and $c = k_{-1}/K_3k_3$.

A reasonably critical test of the kinetic analysis is to examine the dependence of the parameter b from equation (2) (which should represent the rate of proton transfer from solvent to the indole nucleus *i.e.* k_1) on the reactivity of the substrate. This cannot be done directly, however, because the basicity of the 3-position of the indole-3-carboxylic acids is not known but, significantly, an excellent correlation is obtained (Figure 4) between the b values and the rate of protiodetritiation of the parent [3-$^3H_1$]indole at 25°.[3] An interesting point here is that the corresponding datum for azulene [2e] deviates appreciably from the linear plot for indoles, for reasons which remain unclear. Further confidence in the interpretation of equation (2) was obtained by measuring protiodecarboxylation rates for indole-3-carboxylic acid at 60° (Figure 1) and evaluating the enthalpy and entropy of activation for the parameter b. The values obtained ($\Delta H^{\ddagger}$ 83.6 kJ mol^{-1}, $\Delta S^{\ddagger}$ -28 J K^{-1} mol^{-1}) are similar to those obtained for the protonation of indole, itself ($\Delta H^{\ddagger}$ 72.3 kJ mol^{-1}, $\Delta S^{\ddagger}$ -20 J K^{-1} mol^{-1})[14] and, evidently, both processes have similar solvation requirements.

TABLE 1

Values of kinetic parameters a—c [equation (2)] for the decarboxylation of indole-3-carboxylic acids

Indole substituent	Solvent	T/°C	10^7a/s^{-1}	10^4b/l mol^{-1} s^{-1}	c/l mol^{-1}
H	H_2O	25	5.71 ± 1.0	4.54 ± 0.13	20.5 ± 0.76
H	H_2O	60	283 ± 41	174.5 ± 3.4	7.7 ± 0.25
H	D_2O	25	2.23 ± 0.75	1.667 ± 0.023	9.16 ± 0.20
2-Me	H_2O	25	239 ± 72	800 ± 16	58.2 ± 1.3
2-Me	D_2O	25	24 ± 58	340 ± 7.3	27.1 ± 0.76
5-Cl	H_2O	25	1.80 ± 0.64	1.216 ± 0.26	13.45 ± 0.33
5-Cl	D_2O	25	-0.08 ± 0.78	0.545 ± 0.025	6.72 ± 0.39

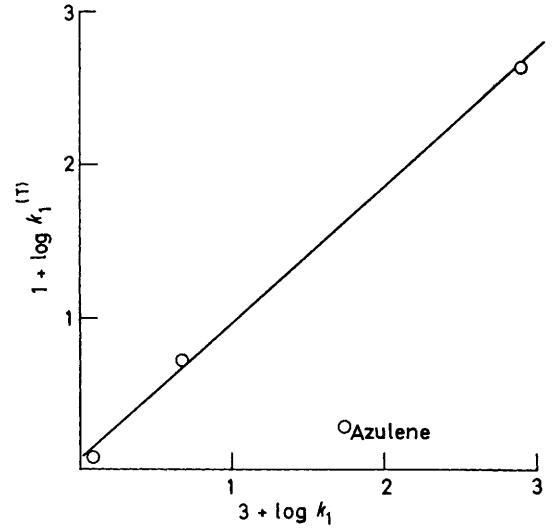


FIGURE 4 Correlation between the rate of protiodetritiation of indoles (Rate = $k_1^{(T)}$[3-$^3H_1$-indole][H_3O^+]) and the rate of decarboxylation (k_1) of indole-3-carboxylic acids at 25 °C

General Acid Catalysis.—Protiodecarboxylation of indole-3-carboxylic acid was also examined in aqueous pyridine buffers at 60° and $\mu = 1.0$ and these results are given in Table 2. Protonation of the substrate, and therefore the rate of decarboxylation, should be subject to general acid catalysis, and equation (4) might be expected as an approximate expression for this catalysis, where [HA] represents the buffer acid concentration. As far as the coefficients a'—c' are concerned, it is no longer certain that these have the same meaning as their counterparts in equation (2), mainly because the inequality $k_3 \gg k_{-2}$ may not remain in the presence of a

$$k_o = (a' + b'[\mathrm{HA}])/(1 + c'[\mathrm{HA}]) \qquad (4)$$

stronger base (A^-) than water (*i.e.* step k_{-2} must be base catalysed and therefore increase in the pyridine buffer solutions). Observed rates of decarboxylation certainly increase with increasing buffer concentration (Table 2), so, qualitatively, general acid catalysis is observed for indole-3-carboxylic acid at 60°, but the extrapolated k_0 value at zero buffer concentration (representing the H_3O^+ catalysed component to the overall rate) listed in Table 2 is of greater interest and more significance. At these low acidities, the terms k_1 [L_3O^+], k_{-1} [L_3O^+], and [L_3O^+]/K_1 all approximate to zero, and, on assuming (as before) that $k_3 \gg k_{-2}$ (^{13}C isotope effects absent), equation (3) reduces to (5).

TABLE 2

Protiodecarboxylation of indole-3-carboxylic acid in H_2O–pyridine buffers at 60° ($\mu = 1.0$ with NaCl)

$[C_5H_5NH^+]$/M	pH_{obs}^{60}	10^5k_o/s^{-1}
0.8	4.81	1.99
0.3	4.83	1.76
0.06	4.83	1.27
0.0		1.2
0.01	5.84	0.352
0.006	5.88	0.297
0.003	5.88	0.253
0.0		0.21
0.017	5.58	0.591
0.010	5.60	0.468
0.005	5.63	0.369
0.0		0.32

$$k_o = K_2k_2/(1 + K_2/[L_3O^+]) \qquad (5)$$

From experiments in dilute HCl, the product K_2k_2 (parameter a) = 2.83×10^{-5} s^{-1} at 60° (Table 1), so the acid dissociation constant (K_2) of indole-3-carboxylic acid can be determined from the extrapolated k_o in pyridine buffers (Table 2) by solution of equation (5). The results of this calculation are summarised in Table 3, where good agreement between K_2 values for each

---

[14] R. Iqbal and B. C. Challis, to be published.

of the three pyridine buffer ratios examined is apparent. Further, the average pK_2, *ca.* 4.7 at 60° and $\mu = 1.0$, is of the same order of magnitude as the extrapolated results of Melzer[13] (measured in aqueous EtOH at 25°). Thus these findings also vindicate the kinetic analysis of the experimental data.

TABLE 3

Evaluation of the equilibrium constant K_2 for indole-3-carboxylic acid at 60°

$10^5k_o/s^{-1}$	$10^5[H_3O^+]/M$	$10^5K_2/M$
1.2	1.5	2.0
0.32	0.26	1.6
0.21	0.13	2.0

Solvent Deuterium Isotope Effects.—Isotopic ratios were calculated for each of the constants *b* and *c* of equation (2) for all three substrates and also for *a* for indole-3-carboxylic acid. Standard errors were propagated in accordance with $\sigma_{x/y}^2 = \sigma_x^2/y^2 + \sigma_y^2x^2/y^4$ and the results are summarised in Table 4. Primary isotope effects resulting from proton transfer from the hydronium ion are expected to have a maximum value of *ca.* 3.6,[15] and those in Table 4 range from 61 to 76% of this figure. Their magnitudes, however, ought to be considered within the context of the full rate expression [equation (3)] with due regard to the relative magnitudes of the coefficients k_{-2} and k_3. As discussed above, if $k_3 \gg k_{-2}$, parameter *b* of equation (2) accurately represents the rate of proton transfer k_1. Conversely, if $k_3 \ll k_{-2}$, equation (3) under moderately acidic conditions (*i.e.* $[L_3O^+]/K_1$ and $K_2/[L_3O^+] \ll 1$) reduces to equation (6) in which the coefficient of $[L_3O^+]$ in the numerator

$$k_o = \frac{K_2k_2 + k_1[L_3O^+]}{1 + k_{-1}[L_3O^+]/K_3k_{-2}} \cdot \frac{k_3}{k_{-2}} \qquad (6)$$

[parameter *b* of equation (2)] equals k_1k_3/k_{-2}. The solvent deuterium isotope effect on *b* in these circumstances assuming that k_3 is solvent independent [equation (7)] might then be expected to lie within the range 2.3/7—3.6/7 (*i.e.* 0.33—0.51) assuming a 90% C–H isotope effect for the k_{-2}^D/k_{-2}^H ratio. This extreme situation is clearly not found in the present instance, but, nonetheless, an exact interpretation of the magnitudes of the isotopic ratios in Table 4 is difficult unless $k_3 \geqslant 10k_{-2}$.

$$b(H_2O)/b(D_2O) = (k_1^H/k_1^D)(k_{-2}^D/k_{-2}^H) \qquad (7)$$

Measurement of ^{13}C isotope effects for decarboxylation would resolve this question, but an alternative approach is to consider the magnitude of $c(H_2O)/c(D_2O)$. We have already shown that the composition of *c* [equation (2)] depends on the relative magnitudes of coefficients k_3 and k_{-2} and equations (8) and (9) for the isotope ratio follow for each of the two extreme cases. Evaluation of the two isotopic ratios assuming a 90% C–H isotope effect for proton loss from (1) and (2)

For $k_3 \gg k_{-2}$

$$c(H_2O)/c(D_2O) = (k_{-1}^H/k_{-1}^D)(K_3^{D_2O}/K_3^{H_2O}) \qquad (8)$$

For $k_3 \ll k_{-2}$

$$c(H_2O)/c(D_2O) = (k_{-1}^H/k_{-1}^D)(k_{-2}^D/k_{-2}^H)(K_3^{D_2O}/K_3^{H_2O}) \qquad (9)$$

(*i.e.* $k_{-1}^H/k_{-1}^D \simeq k_{-2}^H/k_{-2}^D$ *ca.* 7) and a solvent isotope effect of 3 for the equilibrium between (1) and (2) (*i.e.* $K_3^{H_2O}/K_3^{D_2O} = 3$)[16] gives $c(H_2O)/c(D_2O)$ *ca.* 2.3 for $k_3 \gg k_{-2}$ and $c(H_2O)/c(D_2O)$ *ca.* 0.33 for $k_3 \ll k_{-2}$. Significantly, the observed $c(H_2O)/c(D_2O)$ ratios are *ca.* 2.2 (Table 4).

TABLE 4

Deuterium solvent isotope effects for the protonation of aromatic substrates at 25°

Substituents	$a(H_2O)/a(D_2O)$	$b(H_2O)/b(D_2O)$	$c(H_2O)/c(D_2O)$	$10^3k_1/l\ mol^{-1}\ s^{-1}$ [a]
Indole				
3-CO_2H	2.56 ± 0.53	2.72 ± 0.09	2.24 ± 0.09	0.454
2-Me,3-CO_2H		2.35 ± 0.07	2.15 ± 0.08	80.0
5-Cl,3-CO_2H		2.23 ± 0.11	2.00 ± 0.13	0.122
2-Me		2.59 [b] (2.86) [c]		41 000
5-CN		2.60 [d] (2.87) [c]		5.27
3-H				500
5-Cl				118
Azulene				
1-CO_2H		2.5 [e]	2.2 [e]	5.39 [e]
1-H				183 [f]

[a] For non-carboxylic acid substances k_1 is the rate of protiodetritiation, *i.e.* Rate = $k_1^{(T)}[\text{Substrate}][H_3O^+]$. [b] Solvent isotope effect for hydrogen exchange evaluated by the method of A. J. Kresge and Y. Chiang (*J. Amer. Chem. Soc.*, 1962, **84**, 3976) from ref. 3. [c] Values in parentheses are corrected for secondary isotope effects according to ref. 8. [d] From ref. 14. [e] From ref. 2e [f] From J. Schulze and F. A. Long, *J. Amer. Chem. Soc.*, 1964, **86**, 331.

Thus, if the inequality $k_3 \gg k_{-2}$ reverses, the solvent isotope effects on both *b* and *c* should decrease from *ca.* 2.3—2.7 to 0.3. In practice, only one ratio for 5-chloroindole-3-carboxylic acid is slightly low, where $c(H_2O)/c(D_2O) = 2.00 \pm 0.13$ suggests k_3 *ca.* $5k_{-2}$ for this compound. This deduction has two consequences. First, it increases the primary deuterium isotope effect on step k_1 from an observed value of 2.23 to *ca.* 2.6, bringing it into line with other results, and, secondly, it predicts a small carbon isotope effect of *ca.* 1.007 (assuming a maximum value of 1.04) for the ratio $b(^{12}C)/b(^{13}C)$ for 5-chloroindole-3-carboxylic acid.

Although reliable solvent isotope effects are obtained for parameters *b* and *c* of equation (2), the corresponding ratio for *a* is far less accurate. Only for indole-3-

---

[15] C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Amer. Chem. Soc.*, 1965, **87**, 1553.

[16] B. M. Lowe and D. G. Smith, *J.C.S. Faraday I*, 1974, 362.

carboxylic acid is the standard error less than the ratio. These substantial errors are a consequence of *a* representing a very small, but finite, decarboxylation rate at zero [L_3O^+]. The observed ratio for indole-3-carboxylic acid [$a(H_2O)/a(D_2O) = 2.56 \pm 0.53$] is, in fact, considerably lower than the value of *ca.* 9 expected for the product $(k_2^H/k_2^D)(K_2^{H_2O}/K_2^{D_2O})$ [*cf* equation (2)] comprising a primary isotope effect of *ca.* 3 for proton transfer from the solvent to the carboxylate anion and an equilibrium solvent isotope effect of *ca.* 3 for the formation of this anion.[16] The low observed value can be rationalised by the coexistence of a homolytic decarboxylation pathway, which would also manifest itself as a finite rate at zero [L_3O^+]. Since the isotope effect for homolysis should be much lower than for the proton transfer, a reduced value for the ratio $a(H_2O)/a(D_2O)$ is not unexpected.

Conclusions.—Values of $b(H_2O)/b(D_2O)$ for the indole-3-carboxylic acids, when considered with Longridge and Long's [2e] datum for azulene-1-carboxylic acid and other results for the protonation of indole compounds,[3] provide solvent isotope effects for proton transfer from solvent to substrates of widely differing reactivity (Table 4). There is no systematic variation of the isotopic rate ratio with substrate reactivity and all the ratios are remarkably similar if the correction discussed above is applied to the datum for 5-chloroindole-3-carboxylic acid. Over the range of reactivity of *ca.* 10^6 considered here, we conclude that primary isotope effects are but little influenced by substrate reactivity and, *inter alia*, by the symmetry of the transition state for proton transfer.

EXPERIMENTAL

Substrates and Reagents.—Labelled substrates were prepared from the parent indole and $^{14}CO_2$ (obtained from $Ba^{14}CO_3$ supplied by the Radiochemical Centre Ltd.) by carboxylation of the indolylmagnesium Grignard reagent [13,17] using standard vacuum line techniques. Details have been given elsewhere.[18] The procedure gave the required indole-3-carboxylic acid contaminated by significant amounts of the corresponding 1-carboxylic acid, which were removed by heating the solid product to $\leqslant 70°$ for *ca.* 6 h. Independent measurements showed that under acidic conditions indole-1-carboxylic acids underwent decarboxylation *ca.* 20-fold faster than the 3-acid. As a further precaution against the presence of any indole-1-carboxylic acid contaminant, care was taken not to monitor the kinetic reaction solutions before all the 1-acid had decarboxylated.

AnalaR HCl, NaCl, and potassium hydrogen phthalate were used without further purification other than vacuum drying where appropriate. Solutions of DCl were prepared by dissolving purified HCl gas in D_2O (99.7% D; N.M.R. Ltd.).

Kinetics.—Typically, a stock aqueous solution (1 ml) of the sodium indole-3-carboxylate was added to a reaction solution in a volumetric flask containing the appropriate amount of HCl (or DCl) maintained at an ionic strength of 1.0 by addition of NaCl and at 25 or 60° (±0.1°) by immersion in a thermostatted tank. Portions (8 × 10 ml) of this solution were removed at intervals and the reaction quenched by shaking for 1 min with xylene–ethyl acetate (15 ml; 4 : 1 v/v). After 15 min, 10 ml of the organic layer containing unchanged labelled indole-3-carboxylic acid was removed, scintillator solution [5 ml; PPO (4 g l^{-1})–POPOP (0.1 g l^{-1}) in xylene] added and then air was passed through this solution for 5 min to remove $^{14}CO_2$ and to clear the solution. These samples were radioassayed with a Beckmann LS 200 liquid scintillation counter for at least 5×10^4 counts. First-order rate coefficients k_0 were obtained either from equation (10) by plotting or from equation (11) by non-linear least squares analysis, where C_t and C_∞ are the counts min^{-1} at time *t* and ∞, respectively. Kinetic experiments in solvent D_2O followed the same, but scaled-down, procedure using 25 ml reaction solutions and taking 8 × 2 ml portions. The acidity of the reaction solutions was determined volumetrically by titration against B.D.H. standardised NaOH using Bromophenol Blue indicator.

$$\ln (C_t - C_\infty) = b - k_0 t \qquad (10)$$

$$C_t = C_\infty + e^{(b - k_0 t)} \qquad (11)$$

A typical kinetic run, analysed *via* equation (11) is given in Table 5. Errors in k_0 were typically 1—3% by this procedure, a value of ± 2.5% together with an estimated error of $\pm 10^{-3}$N in the acid concentration being used in weighting the observations.

TABLE 5

Deuteriodecarboxylation of 5-chloroindole-3-carboxylic acid at 25° ([D_3O^+] = 1.016M, $\mu = 1.0$ with NaCl)

t/min	Counts min^{-1}	Counts min^{-1} (calc.)	Reaction (%)
0	10 113	10 088	0
1 050	6 466	6 468	36.1
2 505	3 520	3 502	65.2
3 045	2 770	2 792	72.6
3 930	1 909	1 930	81.1
4 395	1 594	1 591	84.2
5 460	1 043	1 027	89.7
6 960	561	564	94.5
∞	0	45 ± 14	100

$k_0 = 7.01 \pm 0.07 \times 10^{-6}\ s^{-1}$.

TABLE 6

Analysis of Longridge and Long's [2e] data for the protiodecarboxylation of azulene-1-carboxylic acid in H_2O at 25° ($\mu = 1.0$)

[H_3O^+]/M	$10^5 k_0/s^{-1}$	$10^5 k_0$ (calc.)	Weight
0.001 02	0.575	0.474	3.8
0.002 96	1.57	1.43	4.5
0.010 0	4.33	4.28	7.7
0.020 0	7.08	7.20	12.6
0.030 0	9.11	9.29	15.2
0.060 0	13.12	13.09	13.6
0.100 0	16.05	15.64	9.5
0.030 0	19.83	19.42	6.4
0.500 0	19.76	20.40	6.4

$a = -6.3 \pm 36 \times 10^7\ s^{-1}$; $b = 5.39 \pm 0.32 \times 10^{-3}$ l mol^{-1} s^{-1} (lit.,[2e] 5.8×10^{-3}); $c = 24.4 \pm 1.7$ l mol^{-1} (lit.,[2e] 26.3).

Analysis of Data.—Equation (2), which expresses the dependence of k_0 on [L_3O^+] was solved for *a*—*c* by non-linear least squares regression analysis using the weighting term (L_i) defined by Deming [19] and Wentworth.[11] Using the errors in k_0 and [L_3O^+] given above, L_i is given by

---

[17] S. Kasparek and R. A. Heacock, *Canad. J. Chem.*, 1967, **45**, 771.

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

[19] W. E. Deming, 'Statistical Adjustment of Data,' Wiley, New York, 1943.

equation (12). Initial values for the iterative procedure

$$L_i = (b - ac)^2/(1 + c[L_3O^+])^4 + 625\,(k_0)^2 \qquad (12)$$

were obtained by linear multiple regression analysis of equation (2) rearranged as equation (13). The complete

$$k_0 = a + b[L_3O^+] - ck_0[L_3O^+] \qquad (13)$$

analytical procedure was tested with the data reported for azulene-1-carboxylic acid by Longridge and Long[2e] and good agreement was obtained (Table 6).

We thank the Salters Company for a scholarship to H. S. R. and the S.R.C. for an equipment grant.

[5/836 *Received, 5th May*, 1975]