Kinetics and Mechanism of N–H and C–H Isotopic Exchange in Pyrrole and Indole: Acid-catalysed Exchange in Aqueous Acetonitrile Solutions

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The deuteriodeprotonation of the N–H and of the α- and β-C–H positions in pyrrole, and of the N–H and β-C–H positions in indole, has been studied kinetically as a function of the concentration of perchloric acid, medium composition, and temperature in aqueous (^2H_2O) acetonitrile solutions. The N–H exchange process was followed using the first overtone of the N–H stretching mode. Ancillary i.r. studies define the molecular states of the reactants. The Hammett H_0 acidity function is reported for dilute perchloric acid in acetonitrile–water mixtures. Bunnett w values clarify differences between the hydration of the N–H and C–H exchange transition states.

Acid-catalysed hydrogen exchange reactions represent the most elementary electrophilic substitution. Ample evidence exists that protic solvent molecules participate in the fast proton-transfer reactions of amines.[1] However, the slow acid-catalysed exchange reaction of aromatic hydrogen usually proceeds *via* an A–S_E2 mechanism, with a rate-determining proton transfer to the substrate.[2,3] Much recent work attempts to correlate the rate of hydrogen exchange with H_0 acidity function studies.[3]

In pyrrole and indole, protonation and exchange can occur not only at the weakly basic nitrogen atom, but also at basic carbon atoms within the aromatic system. Indeed, measurements at equilibrium have shown that pyrrole undergoes protonation mainly at the C_α position[4] (pK_a −3.5) and indole at the C_β position[4] (pK_a −3.8). The nitrogen basicity of pyrrole and indole has been estimated[6] to be much less than their carbon basicity (p$K_a \leq -6$). Challis and Millar[7] have established that hydrogen exchange of indole at C_β proceeds *via* the usual A–S_E2 mechanism but were unable to determine the transition-state symmetry of this reaction as measurements of both the Brönsted exponent and kinetic isotope effects proved unsatisfactory indices of the extent of hydrogen transfer. The role of water in the exchange process has not been considered. The N–H exchange process is expected to be slow and comparable in rate with the C–H exchange process, and it is of interest to compare its mechanism and solvation requirements with those of the similar reactions of amines and C–H groups in aromatic systems. Early work by Koizumi and Titani[8] showed that N–H exchange was much faster than C–H exchange, but we now find that in mixtures of ^2H_2O and aprotic solvents, N–H exchange is sufficiently slow to be followed using the first overtone of the N–H stretching mode. Exchange on carbon is 10—1 000 times slower, and was readily followed by n.m.r. All the hydrogen atoms in pyrrole, but only the N–H and C_β hydrogens in indole, exchange under the mildly acidic conditions used.

In the ^2H_2O–acetonitrile–$HClO_4$ system chosen, a variation of the solvent composition changed both the activity of the water and also the effective acidity of the solution. The acidity of such solutions was quantitatively studied using *m*- and *p*-nitroanilines as indicators. Direct comparison of H_0 with the rates of exchange enabled the solvation of the transition state relative to the anilinium ions to be deduced.

EXPERIMENTAL

Purification of Materials.—Reagents were of commercial AnalaR grade and their m.p.s. or b.p.s. corresponded to literature values after purification.

Acetonitrile from Fluka Ltd. was successively dried over calcium chloride, calcium hydride, and phosphorus pentoxide and freed from acidic, basic, and salt-like impurities. Our methods resembled those of Kolthoff and Chantooni.[9] Water concentrations were determined by Karl Fisher titration and found to be 0.005% after two distillations. Ammonium acetate plus ammonia concentrations were estimated from the absorption at 420 nm of a 10^{-4}M-solution of picric acid in the solvent examined, after allowing for the effect of water. The total ammonia in the solvent was typically 5×10^{-6}M after two distillations and removal of the first fraction. Purified acetonitrile was stored at 0° under nitrogen. Pyrrole was purified by distillation at 30° and 2 mmHg, followed by repeated freeze–thaw degassing and distillation at 10^{-4} mmHg. It was collected as a solid at −78° and stored in ampoules in the dark at −20°. Both pyrrole and indole are slowly oxidised in air and light to give basic products.[10] Indole was sublimed at 45° and 10^{-3} mmHg and recrystallised from redistilled light petroleum (b.p. 40—60°) after discarding any oily material which separated first. It was stored in the dark at −20°. Aniline and substituted aniline indicators were redistilled or sublimed. Perchloric acid (70% v/v) was used without

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further purification. Water [^2H_2O (99.8%)] was boiled and cooled under nitrogen to remove ammonia. Methan[^{2}H]ol was used as received.

Pyrrole–Acetonitrile–Water Associations in Solution.—The solvation of pyrrole in aqueous acetonitrile solutions was deduced from i.r. measurements using a Perkin-Elmer model 257 spectrophotometer and calcium fluoride cells. In carbon tetrachloride pyrrole shows N–H stretching bands at 3 498 (monomer) and 3 420 cm^{-1} (dimer). Addition of acetonitrile increases the absorption at 3 420 cm^{-1} as pyrrole forms a 1 : 1 complex with acetonitrile[11] (K_{ass} *ca.* 3.5 l mol^{-1}). In anhydrous acetonitrile pyrrole shows only one N–H band at 3 420 cm^{-1}, unaffected by dilution, but as water is added this band shifts to 3 360 cm^{-1} and broadens (half-height width 110 cm^{-1}) in accordance with the formation of a N–H · · · O bond. The association constant for the pyrrole–water complex was estimated to be 0.5—2 l mol^{-1}. (The addition of dioxan to a solution of pyrrole in carbon tetrachloride similarly caused the appearance of a N–H · · · O band at 3 360 cm^{-1}.) Indole exhibited parallel behaviour. We conclude that in aqueous acetonitrile of >0.05 mole-fraction, both indole and pyrrole are present as a weakly hydrogen-bonded complex with water, itself hydrogen-bonded to acetonitrile as the receptor.

Kinetics.—For the N–H exchange reactions, 0.16M-solutions of pyrrole or indole in acetonitrile were examined at the N–H stretching overtone at 1.48 μm (ε *ca.* 0.3) in a water-jacketted cell of 10 cm pathlength using a Cary model 14M spectrophotometer. A known excess of ^2H_2O was then added and the rate of exchange of N–H observed. For pure reagents the uncatalysed exchange rate is very low ($k < 5 \times 10^{-5}$ s^{-1}). Proton exchange was initiated by adding appropriate quantities of perchloric acid from a Hamilton microlitre syringe. Typically 15—60 points covering 4—5 half-lives per run were evaluated as a pseudo-first-order reaction using the method of Guggenheim.[12] Generally correlation coefficients were >0.998 and the calculated uncertainties in the slope of the line of best fit were small relative to those introduced by a small (*ca.* 1°) temperature gradient along the cell and by adventitious trace acidic or basic impurities.

For C–H exchange reactions the rate was determined directly in aqueous acetonitrile using a Varian model HA100 n.m.r. spectrometer. Conditions and concentrations were similar to those used for studying the N–H exchange reaction, and the first-order decrease in the integrated proton signals was followed. In acetonitrile, indole exhibits a complex spectrum, but the C_β proton signal at τ 3.35 is well separated and readily distinguishable from the remaining aromatic pattern. The C_α and aromatic protons do not exchange under the conditions used, and to compensate for instrumental fluctuations we measured the ratio of the integral of the C_α–H signal to that of the C_α–^{1}H and aromatic proton signals. The complex spectrum of pyrrole[13] approximates to two quartets, with the C_α protons absorbing at τ 3.15 and the C_β protons at 3.80. The imino-proton signal appears as a very broad line at low field, owing to quadrupole coupling. The exchange of all the C–H in pyrrole was followed relative to an internal standard (cyclo-octa-1,5-diene) whose non-exchanging olefinic protons absorb at τ 4.10. Temperatures were measured to within 0.5° by utilising the temperature dependent chemical shift of the methanol O^{1}H proton with respect to the methyl protons in a separate sample. Isothermal kinetic measurements were made at the normal probe temperature (31—32°).

Representative kinetic runs are shown in Figure 1. In all over 100 rate constants were evaluated; a representative series of runs is given in Table 1, and the remainder, tabulated in a thesis,[14] are available on request.

Acidity Measurements.—Two indicators, *m*- and *p*-nitroaniline, sufficed for the limited range of acidities encountered; measurements were made at one wavelength only, the absorption maximum of the neutral molecules, and the degrees of protonation P were calculated from the equation $P = \log\ (\varepsilon_{BH^+} - \varepsilon)/(\varepsilon - \varepsilon_B)$. For nine different mixtures of ^2H_2O and acetonitrile (with mole fractions of water varying from 0.005 to 0.80) and for six different mixtures of CH_3O^1H and acetonitrile (with mole fractions of methanol between 0.025 and 0.38) the P *versus* log c plots, for perchloric acid at c mol l^{-1} (c 0.001—0.02) were, within experimental error, linear with unit slope. As perchloric acid behaves simply even in anhydrous sulpholan,[15] this was the expected result. The difference in basicity between the two nitroanilines, at mole fractions (^2H_2O) of 0.05 and 0.80 was 1.55 ± 0.1, as expected from the similar difference of 1.4 in water,[16] but in contrast to *ca.* 0.4 in anhydrous

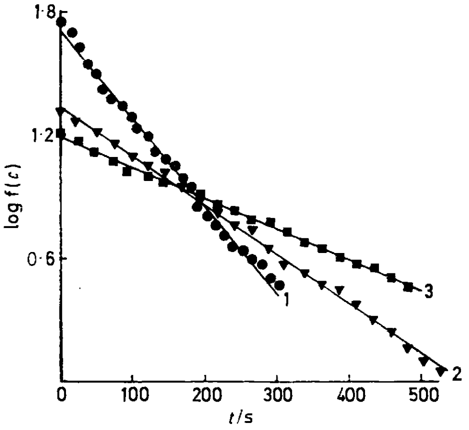

FIGURE 1 Guggenheim plots for pyrrole N–H exchange in ^2H_2O–acetonitrile catalysed by 1.10^{-2}M-perchloric acid: 1, 3.8 mol % (0.77M), rate $(4.29 \pm 0.08) \times 10^3$ s^{-1}; 2, 5.5 (1.1), $(2.40 \pm 0.015) \times 10^3$; and 3, 8.0 (1.65), $(1.50 \pm 0.014) \times 10^3$

TABLE 1

Rates of N–H exchange of pyrrole at 27° in 25 mol % ^2H_2O–acetonitrile catalysed by perchloric acid

$10^3[HClO_4]$/M	$10^3k/s^{-1}$	No. of readings	Correlation coefficient
0	<0.05		
1.0	1.01 ± 0.01	19	0.9988
2.0	2.35 ± 0.02	35	0.9982
3.0	3.76 ± 0.05	27	0.9982
4.0	4.54 ± 0.04	21	0.9994
5.0	5.79 ± 0.04	34	0.9991
7.0	8.85 ± 0.06	27	0.9993
9.0	10.18 ± 0.18	22	0.9968

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sulpholan.[15] However, the main interest lay in the relationship of P to solvent composition at constant acid concentration.

RESULTS AND DISCUSSION

(a) *Kinetics.*—Perchloric acid is reported to be fully dissociated in even anhydrous acetonitrile,[17] and therefore in aqueous acetonitrile it represents the oxonium ion. With this catalyst the rates of exchange of hydrogen at corresponding sites in pyrrole and indole underwent parallel changes on changing either the acid concentration or the solvent composition. Indole proved to be more reactive, and representative relative rates are shown in Table 2.

TABLE 2

Kinetics of C–H and N–H hydrogen exchange in indole and pyrrole in ^2H_2O–acetonitrile mixtures catalysed by perchloric acid

(a) Relative rates of hydrogen exchange at 27°. $[HClO_4] = 4 \times 10^{-3}$ M

	Pyrrole			Indole	
Mol % (M)	N–H	C_α–H	C_β–H	N–H	C_β–H
7.5 (1.5)	14	1.25	1.4	2 400	8
10 (2.0)	10	0.9	1 [a]	2 000	5
26 (6.0)	5.5	0.22	0.25	1 000	1.3

(b) Activation parameters of hydrogen exchange; 10 mol % ^2H_2O–CH_3CN

	Pyrrole			Indole	
	N–H	C_α–H	C_β–H	N–H	C_β–H
$\Delta H^{\ddagger}$ [b]	75 ± 1	80 ± 2	80 ± 2	61 ± 2	69 ± 6
$\Delta S^{\ddagger}$ [c]	−37 ± 4	−33 ± 5 [d]	−32 ± 5 [d]	−83 ± 7	−76 ± 20
No. of points	8	3	3	8	3

[a] $k = 10^{-3}$ s^{-1}. [b] Units are kJ mol^{-1}. [c] Units are J K^{-1} mol^{-1}. [d] Includes a statistical correction.

A linear dependence on the acid concentration was shown for all exchange reactions and at different solvent compositions (*e.g.* Table 1), although a correction for traces of basic contaminants in the reagents was necessary especially at the low acid concentrations (*ca.* 5×10^{-5}M) required for studying the indole N–H exchange. Significantly, the rate dropped sharply as the water concentration was increased, and changes in the solvent composition at constant $HClO_4$ concentration did *not* produce parallel changes in the N–H and C–H exchange rates (Table 2 and see later). In strongly aqueous solutions (*ca.* 50 mol %) the C–H and N–H exchange rates pass through broad minima. In pure ^2H_2O, the rate of C_β–H exchange in indole was similar to that in solutions of 10 mol % ^2H_2O–CH_3CN and is in agreement with the rate of hydrogen exchange of [3-$^2H_1$]indole in dilute hydrochloric acid reported by Challis and Millar.[7] Changing the solvent to CH_3O^2H–CH_3CN enhanced the rate of N–H exchange *ca.* 10-fold, presumably owing to the greater activity of the methanol-solvated proton compared to the oxonium ion.

Activation parameters were determined for all the exchange reactions and are presented in Table 2. Enthalpy values are consistent with the relative reactivity and electron density at the various exchange sites in pyrrole and indole but the similarity of entropy values observed for the N–H and C–H exchange in each substrate requires consideration.

The proposal by Long and Schaleger,[18] that the entropy of activation decreases by *ca.* 20 J K^{-1} mol^{-1} for each water molecule frozen in the ionisation process, is widely accepted. Oxonium ions are strongly solvated in aqueous solutions with each proton believed to be associated with four molecules of water of solvation.[19] This is also true in dilute ($\geq$0.5M-H_2O) aqueous acetonitrile solutions.[20] Protonated aromatic species are hydrated to a much smaller extent.[21] Thus the protonation of aromatic substrates by oxonium ions is accompanied by the release of solvating water molecules and a positive contribution to $\Delta S^{\dagger}$. This release of water will vary according to the extent of proton transfer in the transition state. The protonation and deprotonation of azulene proceeds with quite different values of $\Delta S^{\dagger}$.[22]

Indole and pyrrole are much more basic at carbon than at nitrogen. Indeed, the heat of formation of *N*-protonated pyrrole is calculated to be *ca.* 33 kJ mol^{-1}, greater than that of C_α-protonated pyrrole.[23] Thus the transition state for N–H exchange should approximate more closely to the protonated intermediate than the transition state for C–H exchange [24] and result in more extensive desolvation of the oxonium ion. The observation that the entropies of activation of C–H and N–H exchange in indole and pyrrole are similar (Table 2) suggests that the N–H exchange process requires water molecules in the transition state.

(b) *Equilibrium Measurements.*—We first examined acidity functions in this system, using primary amines for convenience. The behaviour of the ^2H_2O–acetonitrile–$HClO_4$ system closely paralleled many others consisting of a mineral acid in mixtures of water and an organic solvent,[25] typified by Braude and Stern's classical work on the system H_2O–EtOH–HCl.[26] As shown in Figure 2, a broad minimum was found at *ca.* 50 mol % with the acidity increasing at low concentrations of water, as (in Bell's interpretation) the $H_3O^+,3H_2O$ cation was replaced by more acidic lower hydrates.[19] The acidity rose more rapidly at low ^2H_2O concentrations in the CH_3CN–^2H_2O system, as would be expected in view

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of the much lower basicity of acetonitrile as compared with ethanol. In the system CH_3O^1H–acetonitrile–$HClO_4$ a similar curve was observed (Figure 2), at least in the acetonitrile-rich zone, and the displacement downwards in $-H_0$, *ca.* 0.8 units,* corresponds closely to that observed for pure methanol *versus* pure water.[19] Thus mixtures of acetonitrile and protic solvents behave like the corresponding pure protic solvent–acid system.

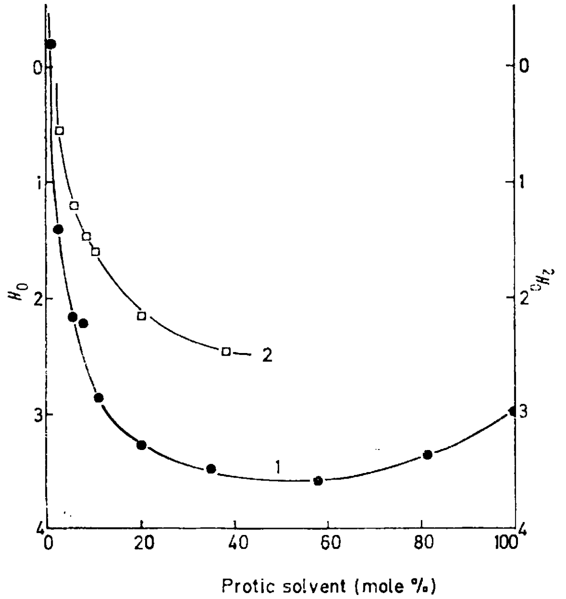

FIGURE 2 Variation of H_0 with composition of ^2H_2O– and CH_3OH–acetonitrile solutions with [$HClO_4$] 10^{-3}M: 1, solvent is ^2H_2O–CH_3CN; 2, CH_3OH–CH_3CN; $p^2H = pH + 0.4$ (ref. 27)

The acidic solutions used were so dilute that the molecular state of the water should approximate to that of the corresponding binary system. Water is undoubtedly depolymerised in dilute solutions in acetonitrile, as indicated by a large negative heat of solution and by the replacement of the broad O–H stretching absorption by two bands at 3 650 and 3 560 cm^{-1}. Vapour-pressure measurements for the binary system have been published,[28] and activities calculated; we here neglect any differences between ^1H_2O and ^2H_2O in activity coefficient at any given composition. The binary system is non-ideal; the activity of water remains about constant in 25—80 mole % aqueous acetonitrile solutions.

(c) *Correlation of Kinetic and Equilibrium Studies.*—There is the possibility that these exchange reactions, like certain solvolyses, have intrinsic rates which change rapidly with solvent composition. We do not adopt this hypothesis, because in these exchange processes no very large change in the degree of concentration and/or separation of electrical charge is probable. Parker[29] finds only a small solvent effect on changing from a dipolar aprotic solvent to a protic solvent for reactions of cations with polar neutral molecules. Acetonitrile solvates cations very poorly and water preferentially solvates both cations and cationic transition states in aqueous acetonitrile. We conclude that the kinetics probably reflect the protonation equilibria and the composition of the transition states.

In most investigations aimed at determining the role of water in an acid-catalysed reaction, aqueous acidic solutions of high concentration have been used, in which the more rapid increase in $-H_0$ than in the stoicheiometric acidity is attributed to the diminishing activity of water, as successive molecules are lost from the species $H_3O^+,3H_2O$ which predominates in dilute aqueous solution. As Thomas and Leveson[30] said, it should be equally valid to examine reaction rate as a function of water activity and H_0 in a series of solutions of a small and constant concentration of a strong acid, with an aprotic solvent as the bulk component. Indeed, *w* values[31] so obtained should be more precisely determinable, and have much the same significance, as those obtained from concentrated aqueous systems.

The *C*-protonation equilibria of pyrrole and indole closely follow the tertiary amine acidity function H,[4,5,32] which differs slightly from the primary aniline H_0 function in aqueous acids[25] to an extent consistent with a difference of two weakly associated molecules of water of hydration in the respective protonated indicator species InH^+.[25,32] For N–H exchange reactions the *N*-protonation of nitro-anilines could be a better parallel than the *C*-protonation of substituted indoles.

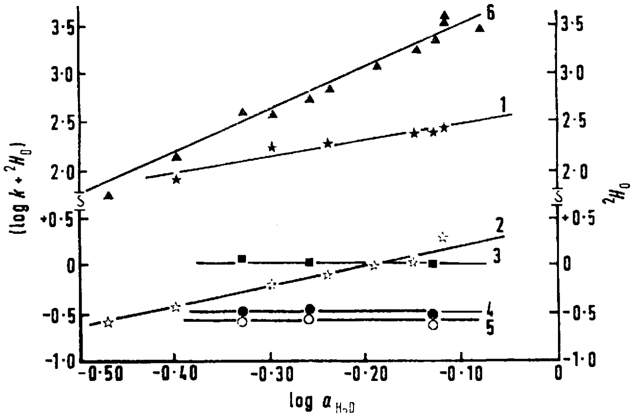

FIGURE 3 Bunnett correlation of $^2H_0$, rate constant, and water activity in ^2H_2O–acetonitrile mixtures with $HClO_4$ 10^{-3}M 1, indole N–H; 2, pyrrole N–H; 3, indole Cβ–H; 4, pyrrole Cβ–H; 5, pyrrole Cα–H; 6, $^2H_0$ function. Experimental points, theoretical lines

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* After correcting to the pH scale,[27] $p^2H = pH + 0.4$.

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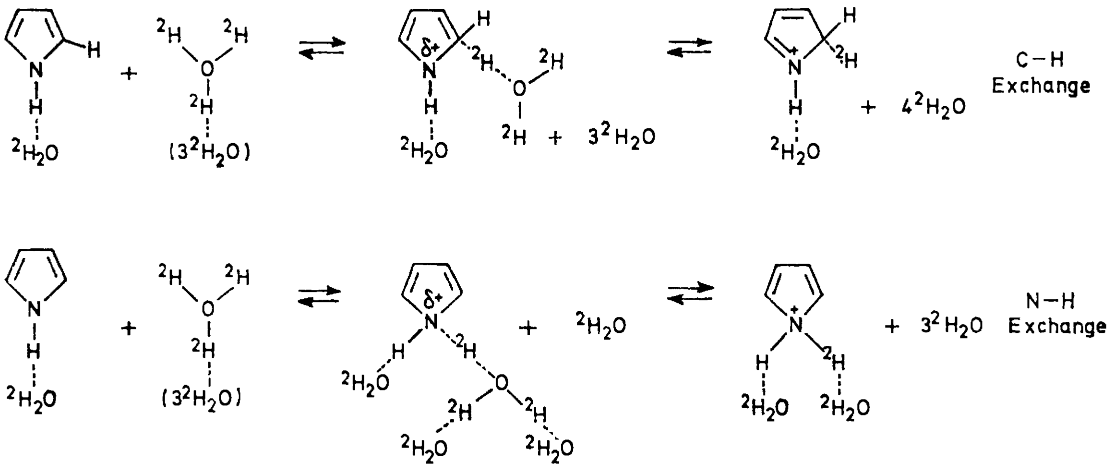
Kolthoff and Chantooni[9] calculate that in aqueous acetonitrile solutions (containing $\geq$0.5M-H_2O), the proton exists mainly as a tetrahydrate. A plot of our ${}^2H_0$ values against log a_{H_2O} [19] gives a good straight line slope of 4.3 ± 0.2 (Figure 3); a slope of 4 would be consistent with H_0 results in concentrated acid–water systems.[27] This indicates that four molecules of water are released as the indicator is protonated by the $H_3O^+,3H_2O$ cation and that the hydration of InH^+ is comparable with the further weak hydration of the $H_3O^+,3H_2O$ cation. Boyd[25] notes that the activity coefficient of the $H_3O^+,3H_2O$ cation is still far from medium-independent but concludes that there is a fortuitous resemblance of the primary hydrated proton and the substituted anilinium cation, leading to some success of hydration treatments for the original Hammett function which are not necessarily as successful for other functions.

When (log $k + {}^2H_0$) for the various exchange processes was plotted against the logarithm of water activity (Figure 3), some very simple relationships were found. For C–H exchange in the three sites investigated (C_α and C_β in pyrrole; C_β in indole), $w = 0$, *i.e.* k/h_0 is independent of water activity; but for both the N–H exchange reactions $w = 2$, *i.e.* k/h_0 is proportional to $[H_2O]^2$. The interpretation of w values[25,31] suggests that for C–H exchange water acts as a proton-transfer agent in the rate-determining step and that the hydration of the transition state is similar to the hydration of the protonated nitroaniline indicator (Scheme), *i.e.* the water associated with the primary hydration shell of the proton is released. Water is believed to be weakly associated with pyrrole and indole in aqueous acetonitrile (see Experimental section).

The w value of 2 for N–H exchange with respect to ${}^2H_0$ suggests that water acts as a nucleophile in the exchange process and that about two more water molecules are associated with the transition state than with the protonated nitroaniline indicator (Scheme). However such plots of (log $k + H_0$) *versus* log a_{H_2O} do not distinguish between chemical participation of water in the transition state and a simple hydration interaction (solvation) in the transition state. One would expect water to be strongly solvated to *N*-protonated pyrrole since it is a stronger acid than H_3O^+. The chemical significance of such hydration changes indicated by w values is discussed by Bunnett[31] and by Boyd[25] and their reservations apply here. Nevertheless it appears that the N–H exchange process in indole and pyrrole is related to the proton-exchange mechanisms for amines in aqueous systems as studied by Grunwald, Alei, and their collaborators[1] where water plays an integral part in the mechanism.



SCHEME

Our observations on the kinetics and mechanism of N–H exchange do not support the view[33] that exchange at nitrogen in indole can take place *via* 3-protonation followed by deprotonation of the resulting 3*H*-indole. For the C–H exchange process, the release of water from the primary solvation shell of the proton in the transition state indicates that the proton is well transferred from the oxonium ion to the pyrrole and indole substrates.

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