

Kinetics and Mechanism of N-H and C-H Exchange in Pyrrole and Indole. Part II.¹ General Acid Catalysed Exchange in Aqueous Acetonitrile

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Rates of hydrogen exchange at N, C_α, and C_β in pyrrole, and at N, and C_β in indole, are reported for various ²H₂O-acetonitrile solutions containing trichloroacetic acid as catalyst. I.r. studies established the molecular state and the approximate pK_a of trichloroacetic acid in this system. The observation of general acid catalysis suggests a common A-S_E2 exchange mechanism for both N-H and C-H exchange reactions. As the solvent composition is changed, the apparent H₀ acidity function, and the rates of C_α-H and C_β-H exchange, do not follow parallel curves because of differences between the hydration of the conjugate acid of the indicator and the transition state for exchange. The relative rate of exchange at C_α and C_β in pyrrole in this system differs significantly from that in the ²H₂O-acetonitrile-HClO₄ system.

TYPICALLY, hydrogen exchange is fast at nitrogen,² and is slow at carbon.³ Pyrrole and indole are carbon bases possessing a weakly basic nitrogen atom. In dilute aqueous acid solutions, protonation and exchange occur at every centre in pyrrole, and at N and C_β in indole.⁴ We have reported that in aqueous (²H₂O) acetonitrile-dilute perchloric acid solutions, the N-H exchange process for these substrates is sufficiently slow to be followed by the decrease in the first overtone of the N-H stretching mode.¹

For the acid catalysed C-H exchange of [3-²H₁]- and [3-³H₁]-indole in ¹H₂O, Challis and Millar have observed general acid catalysis⁵ and established that the usual A-S_E2 mechanism holds, but the mechanism of the N-H exchange reaction has not been considered. Accordingly, using ²H₂O-acetonitrile solutions, we now compare the kinetics, the mechanism, and the role of water, in the N-H and C-H exchange reactions of pyrrole and indole catalysed by the trichloroacetic acid molecule, with previous results for the reaction catalysed by perchloric acid. Buffered solutions were not used, as the solvent is mostly organic and ion-pairing is reported to be extensive in acetonitrile solutions.⁶ In our systems the equilibria involved are not well understood. Instead the contributions to the rate of the various catalysing species in the system were deduced from kinetic observations over a range of solvent compositions in which the dissociation constant of trichloroacetic acid changed markedly. The observed rate of exchange may be expressed as shown in equation (1).

$$k_{\text{obs}} = k_1[{}^2\text{H}_2\text{O}] + k_2[{}^2\text{H}_3\text{O}^+] + k_3[\text{CCl}_3\text{CO}_2{}^2\text{H}] + k_4[\text{CCl}_3\text{CO}_2^-] \quad (1)$$

EXPERIMENTAL

Purification of Materials.—All reagents were purchased as AnalaR or Laboratory Grade from commercial suppliers. The purification of acetonitrile, pyrrole, and indole to remove trace acidic and basic impurities has been previously

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¹ Part I, D. M. Muir and M. C. Whiting, *J.C.S. Perkin II*, 1975, 1316.

² E. Grunwald and M. Cocivera, *Discuss. Faraday Soc.*, 1965, **39**, 109.

³ A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, 1961, **83**, 2877.

described.¹ Water (²H₂O; 99.8%) was boiled and cooled under nitrogen to remove ammonia. Methanol (CH₃O²H) was used as received. Trichloroacetic acid was dried by azeotropic distillation with benzene and recrystallised from the remaining benzene. The filtration was carried out under a stream of nitrogen and the crystals stored in a desiccator over phosphorus pentoxide. *m*-Chloro- and *m*-bromoaniline were distilled at 100° and 10⁻¹ mmHg; aniline was dried over potassium hydroxide and redistilled at 65° and 8 mmHg; *p*-hydroxyaniline was sublimed at 100° and 10⁻¹ mmHg.

I.r. Measurements.—A Perkin-Elmer model 257 spectrophotometer was used with calcium fluoride cells.

Acidity Measurements.—The degree of protonation of aniline and other substituted aniline indicators (above) was measured at the absorption maximum of the neutral molecules using a Cary model 14M spectrophotometer. Degrees of protonation *P* were calculated from the equation $P = \log(\epsilon_{\text{BH}^+} - \epsilon)/(\epsilon - \epsilon_{\text{B}})$.⁷

Kinetics.—N-H Exchange reactions were measured by following the decrease of the first overtone of the N-H stretching mode at 1.48 μm, using the Cary model 14M spectrophotometer. For C-H exchange reactions, the rate was determined directly in a Varian model HA100 spectrometer by following the decrease in the integrated proton signals with respect to an internal standard containing non-exchanging protons. The methods and details have been previously described.^{1,8} A stock solution of 2M-trichloroacetic acid in anhydrous acetonitrile was prepared immediately prior to its use as a catalyst to initiate the N-H and C-H exchange reactions; appropriate quantities were added to the reaction cell after it was established that the uncatalysed rate of exchange was very slow ($k \leq 5 \times 10^{-5} \text{ s}^{-1}$ at 25°). Pseudo-first-order conditions with respect to ²H₂O were maintained for all reactions.

RESULTS AND DISCUSSION

Solutions of pyrrole, indole, trichloroacetic acid, water, and acetonitrile, corresponding to those used in the kinetic study (see later), were examined by i.r. to determine the molecular associations and solvation of the

⁴ M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan*, 1939, **14**, 491 and prior papers.

⁵ B. C. Challis and E. O. Millar, *J.C.S. Perkin II*, 1972, 1618.

⁶ I. M. Kolthoff, S. Bruckenstein, and M. K. Chantooni, *J. Amer. Chem. Soc.*, 1961, **83**, 3927; 1963, **85**, 426.

⁷ R. W. Alder, G. R. Chalkley, and M. C. Whiting, *Chem. Comm.*, 1966, 405; N. C. Evans, Ph.D. Thesis, Bristol, 1968.

⁸ D. M. Muir, Ph.D. Thesis, Bristol, 1970.

reagents in this system, and to determine the extent of dissociation of trichloroacetic acid over a range of $^2\text{H}_2\text{O}$ -acetonitrile compositions.

Solvation of the Reagents.—In aqueous acetonitrile we have found that pyrrole and indole exist as monomers weakly solvated by water, itself hydrogen-bonded to acetonitrile.¹ Trichloroacetic acid in the solid or fused state is a dimer, and on dissolution in carbon tetrachloride it gives solutions having maxima due to monomer and dimer at 1 793 and 1 753 (± 2) cm^{-1} , respectively.⁹ Addition of small quantities of acetonitrile gradually replaces these by a band at 1 781 cm^{-1} , shifting to 1 776 cm^{-1} at 2.5M concentration, when no other carbonyl band can be seen. Parallel changes are seen in the region of hydrogen-bonded -OH absorption, with maxima at 2 630 and 2 490 cm^{-1} being replaced by a broad band at 2 570 cm^{-1} . Thus, trichloroacetic acid exists in such solutions as a monomer hydrogen-bonded to acetonitrile. In pure acetonitrile the carbonyl peak is at 1 773 cm^{-1} , and a prominent band is seen at 1 217 cm^{-1} ; the spectrum is similar to that shown by trichloroacetic acid-dimethyl sulphoxide adducts.^{10,11} When water is added ($^2\text{H}_2\text{O}$), the carbonyl band moves to 1 753 cm^{-1} and a band at 1 257 cm^{-1} replaces that at 1 217 cm^{-1} , the association constant being *ca.* 2 l mol⁻¹. These spectroscopic changes imply the formation of the species $\text{CCl}_3\text{CO}_2^-\text{H} \cdots \text{O}^2\text{H}_2$. Dissociation of trichloroacetic acid occurs as the above solution is further diluted with $^2\text{H}_2\text{O}$; the carbonyl band at 1 757 cm^{-1} is first joined, then replaced by a peak at *ca.* 1 663 cm^{-1} , similar to that shown by sodium trichloroacetate in $^2\text{H}_2\text{O}$. In acetonitrile, the triethylamine salt absorbed at 1 683 cm^{-1} and its extinction coefficient was 1.7 times that of the acid; on the assumption that this ratio was independent of solvent and counter-ion, approximate values of the dissociation constant were calculated (Table 1). We are not aware

TABLE I

Approximate dissociation constant of trichloroacetic acid in aqueous acetonitrile

Molarity of $^2\text{H}_2\text{O}$	Mole fraction	K
0	0	($\sim 10^{-15}$) ^a
2.0	0.10	10^{-6} – 10^{-7}
4.0	0.18	5×10^{-6}
5.5	0.24	3×10^{-5}
6.6	0.28	1×10^{-4}
8.8	0.35	4×10^{-3}
(Pure $^1\text{H}_2\text{O}$)	1.0	5×10^{-1}

^a Ref. 12.

of any previous measurement of the dissociation constant of a carboxylic acid by this very direct method.

A final complexity revealed by i.r. spectroscopy was the formation of a homoconjugate anion $\text{CCl}_3\text{CO}_2^-\text{H} \cdots \text{O}_2\text{CCl}_3$. When a 1:1 mixture of sodium trichloroacetate and trichloroacetic acid was dissolved in anhydrous acetonitrile, no peak at *ca.* 1 680 cm^{-1} was

seen, but rather a broad maximum at 1 770 cm^{-1} and a marked shoulder at 1 740 cm^{-1} . This result is predictable from much work using other techniques,¹² and disappears as water is added to the solution.

Protonation of Aniline Indicators.—Rates of reactions exhibiting the $A-S_{E2}$ mechanism follow the H_0 acidity function, although a precise correlation is determined by the hydration of the protonated indicator and the hydration of the transition state. Acidity functions were therefore determined for a number of mixtures of acetonitrile, $^2\text{H}_2\text{O}$, and trichloroacetic acid (10^{-3} – 10^{-1}M) as typically required for the kinetic studies (see later). This work involved the indicator series, *p*-bromo-, *p*-chloro-, *p*-hydroxy-aniline, and aniline itself. A rigorous investigation of this system would have involved very extensive work indeed; enough was done to show that complications are present.⁸

In anhydrous acetonitrile, plots of degrees of apparent protonation P versus $\log c$ (where c = concentration of acid) were steep (slope *ca.* 1.5) and curved positively, indicating the formation of ion-pairs and homoconjugation of the anion. Slopes near, but significantly exceeding, unity were still found in $^2\text{H}_2\text{O}$ -acetonitrile solutions containing 0.10 mole fraction $^2\text{H}_2\text{O}$. In solutions containing 0.20–0.35 mole fraction $^2\text{H}_2\text{O}$ slopes were typically 0.6–0.8, indicating partial dissociation of the conjugate acid of the indicator. In pure water trichloroacetic acid itself is largely dissociated (Table 1). These results suggest that the aniline indicators form undissociated ion-pairs with the trichloroacetic acid molecule in acetonitrile containing 0–0.2 mole fraction $^2\text{H}_2\text{O}$.

When the concentration of the indicator was held constant at 4.10^{-4}M , and that of the acid fixed at 0.05, 0.01, and 0.002M, while the mole fraction of $^2\text{H}_2\text{O}$ varied from 0 to 0.2, a family of curves was obtained for the apparent 2H_0 which all showed shallow minima (Figure 1), and were quite different from the 2H_0 curve reported for HClO_4 in this solvent mixture.¹ Clearly the curves are not parallel because of the partial dissociation of trichloroacetic acid at low concentrations of acid and various complex equilibria. In 0.10 mole fraction $^2\text{H}_2\text{O}$ the trichloroacetic acid molecule is *ca.* 100 times less effective in protonating the aniline indicator than the hydronium ion.

It has been reported that trichloroacetic acid is split quantitatively into chloroform and carbon dioxide when heated in organic bases such as aniline.¹³ However, subsequent investigations revealed that decarboxylation is a bimolecular reaction of the trichloroacetate anion and the base; un-ionised trichloroacetic acid is stable.¹⁴ In pure aniline the rate of reaction of the anion is slow (k is *ca.* $1.5 \times 10^{-6} \text{ s}^{-1}$ at 25°). We would expect, and find, no evidence of any significant reaction between

¹¹ D. Hadzi and N. Sheppard, *Proc. Roy. Soc.*, 1953, **216**, 247.

¹² J. F. Coetzee, *Progr. Phys. Org. Chem.*, 1967, **4**, 45.

¹³ H. Silberstein, *Ber.*, 1884, **17**, 2664.

¹⁴ L. W. Clark, 'The Chemistry of Carboxylic Acids and Esters,' ed. S. Patai, Interscience, New York, 1969, p. 598.

⁹ M. Flett, *J. Chem. Soc.*, 1951, 962; O. D. Shreve, M. R. Heether, H. B. Knight, and D. Swern, *Analyt. Chem.*, 1950, **22**, 1498.

¹⁰ D. Hadzi and N. Kobilarov, *J. Chem. Soc. (A)*, 1966, 439.

trichloroacetic acid and aniline, pyrrole, or indole in our system.

Kinetics.—We first discuss the exchange reaction of the N-H group in pyrrole, which is relatively easy to

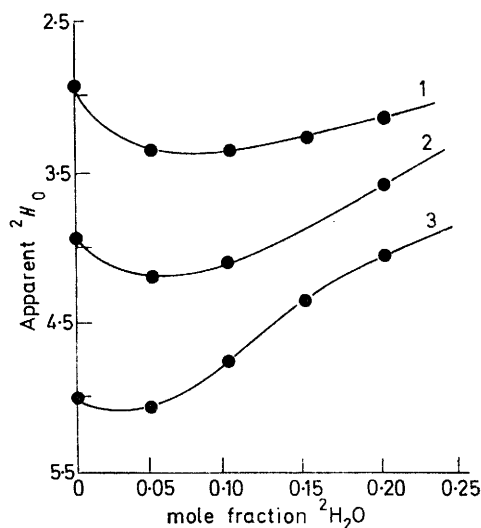


FIGURE 1 Apparent 2H_0 function for trichloroacetic acid in acetonitrile- 2H_2O : [trichloroacetic acid], 1, 0.05M; 2, 0.01M; 3, 0.002M

interpret. A plot of the rate of exchange in $10^{-2}M$ -trichloroacetic acid solutions varying from 0.10 to 0.81 mole fraction of 2H_2O indicates three main features. (i) In very aqueous systems (>0.7 mole fraction) the rate is almost identical to that observed with $10^{-2}M$ -perchloric acid solutions. This implies complete dissociation of trichloroacetic acid, and catalysis by H_3O^+ . (ii) In solutions containing *ca.* 0.22 mole fraction of 2H_2O the rate is much lower than for perchloric acid solutions of the same strength. As the concentration of trichloroacetic acid, c , is varied in such solutions, the rate, k , does not vary linearly (Figure 2). This implies that H_3O^+ is the

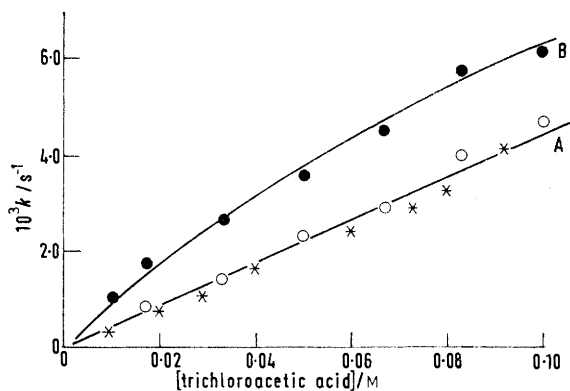


FIGURE 2 Pyrrole N-H exchange rates against trichloroacetic acid concentration in acetonitrile- 2H_2O : Mole fraction 2H_2O , A, 0.10 (*) and 0.025 (O); B, 0.22

main catalyst, with only partial dissociation of trichloroacetic acid (Table 1). (iii) At 0.10 mole fraction of

2H_2O the rate is now only a small fraction (*ca.* 1%) of that observed using perchloric acid. This region was further scrutinised. As shown in Figure 2, in this solution the rate varied linearly with acid concentration. Separate plots (two sets of runs) of $\log k$ versus $\log c$ gave slopes of 1.13 ± 0.03 and 1.10 ± 0.09 . When c was maintained at 0.05M and the water content varied in this region, the rate approached a minimum at 0.05 mole fraction of 2H_2O (Figure 3). The change in rate reflected the change in the apparent 2H_0 function for this system (Figure 1). We conclude that in this solvent region, the rate is catalysed by molecular trichloroacetic acid, *i.e.* the N-H exchange reaction is subject to general acid catalysis.

Once this hypothesis is accepted, the results of varying c in solutions of 0.22 mole fraction of 2H_2O can be profitably re-examined. The rate, now attributed to undissociated trichloroacetic acid, is essentially constant at mole fractions 0.025–0.10 (Figure 3). If we assume that the acid is largely undissociated and that the neutral molecule has the same intrinsic rate at mole fraction 0.22 (as the indicator measurements suggest it should), the observed rate can be roughly partitioned into terms attributable to $CCl_3CO_2^2H$ and to ${}^2H_3O^+$. The term for ${}^2H_3O^+$ can now be treated separately, and then $\partial \log k / \partial \log c$ is found to

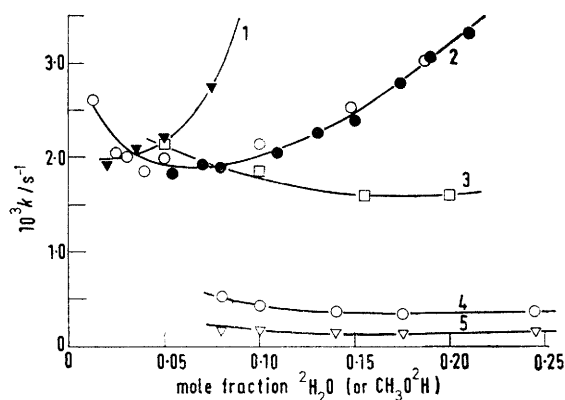


FIGURE 3 Effect of solvent composition on trichloroacetic acid catalysed rates of exchange: exchange site, [trichloroacetic acid], protic solvent used, substrate concentration, 1, Indole N-H, 0.004M, CH_3O^2H , 0.15M; 2, pyrrole N-H, 0.005M, 2H_2O , 0.15M (●) and 0.02M (○); 3, indole C_β -H, 0.04M, 2H_2O , 0.15M; 4, pyrrole C_α -H, 0.05M, 2H_2O , 0.15M; 5, pyrrole C_β -H, 0.05M, 2H_2O , 0.15M

be 0.45 ± 0.06 , in excellent agreement with the Ostwald dilution law. The theoretical line passing through the experimental points is shown in Figure 2. Not only does this consistency strengthen the interpretation given; it also allows an approximate ratio for the rate coefficients for the hydrated hydronium ion and the trichloroacetic acid molecule to be calculated. This was found to be *ca.* 100 at 0.10 mole fraction of 2H_2O ; it will however vary with solutions, H_0 is similar in pure water and in 0.10 mole fraction water-acetonitrile.¹

When this investigation was extended to indole, the greater reactivity of indole enforced much lower concentrations of trichloroacetic acid (typically $5 \times 10^{-4}M$)

which showed significant dissociation at all the solvent compositions studied. We therefore turned to the system acetonitrile- $\text{CH}_3\text{O}^2\text{H}$ -trichloroacetic acid. Here rates were *ca.* 10 times slower than in the corresponding water system and the acid dissociation constant smaller. (For catalysis by the solvated proton, a change from ${}^2\text{H}_2\text{O}$ - to $\text{CH}_3\text{O}^2\text{H}$ -acetonitrile increases the rate *ca.* 10 times.¹) At 0.05 mole fraction of $\text{CH}_3\text{O}^2\text{H}$ a plot of $\partial \log k / \partial \log c$ gave a slope of 1.20 ± 0.11 . Thus the phenomena observed qualitatively resemble the behaviour of pyrrole in aqueous acetonitrile at higher trichloroacetic acid concentrations.

The C-H exchange reactions presented fewer problems. Attention was focused on relatively non-aqueous compositions. For both α - and β -positions in pyrrole, and also for the β -position in indole, plots of $\log k$ versus $\log c$ in 0.10 mole fraction of ${}^2\text{H}_2\text{O}$ had slopes near to unity (experimentally, 0.91 ± 0.03 , and 0.86 ± 0.05). Again, these reactions were much slower than in comparable solutions of perchloric acid and the catalysis is attributed to the $\text{CCl}_3\text{CO}_2^2\text{H}$ molecule. This was the expected result, as general acid catalysis has been confirmed for $\text{C}_\beta\text{-H}$ exchange in indole in aqueous buffer solutions.⁵ Variation of the water concentration (keeping c fixed) indicated no significant increase in rate even at mole fractions of water as high as 0.22. The lower overall reactivity, and the consequent relatively high acid concentration used, naturally facilitates the observation of general acid catalysis in the C-H exchange process.

From the evidence presented so far, it is not possible to quantitatively estimate the catalytic effect of the trichloroacetate anion on the rate of exchange. However, Bell and Jones¹⁵ established that the acetate anion was at least 100 times less effective than the H_3O^+ species in general acid-base catalysed reactions in aqueous solutions. Since the trichloroacetate anion is a much weaker base than the acetate anion, its contribution to the kinetics of N-H and C-H exchange in aqueous acetonitrile must be very small.

Once conditions had been defined for the exchange reaction catalysed by trichloroacetic acid at the carbon atoms of pyrrole and indole and at the nitrogen atom of pyrrole, variation of temperature led to the enthalpies and entropies of activation listed in Table 2. As found for the hydronium ion catalysed process¹ they were self-consistent. There is a much more adverse entropy of activation (difference *ca.* $50 \text{ J K}^{-1} \text{ mol}^{-1}$), and slightly lower enthalpy, when the catalyst is trichloroacetic acid than when the catalyst is the hydronium ion. Directly one can conclude that greater localisation of solvent has occurred at the transition state when the neutral molecule is the catalyst, or that less water is released from the solvation sphere of the trichloroacetic acid molecule than from the proton at the transition state.

The relative rates of hydrogen exchange at N-H and C-H were determined by direct comparison or, for N-H exchange in indole, by extrapolation of results obtained

using lower trichloroacetic acid concentrations. Compared with the rates of exchange catalysed by the hydronium ion, not only is the exchange much slower when catalysed by the trichloroacetic acid molecule, but also the relative rates differ. In pyrrole the relative rate at C_α and C_β (k_α/k_β) was 2.7 (*cf.* 0.85 with perchloric acid¹); whilst the relative rate of N-H exchange in indole and pyrrole (k_i/k_p), was 50 (*cf.* 180 with perchloric acid). For pyrrole in dioxan- ${}^2\text{H}_2\text{O}$ solutions and catalysed by deuterioacetic acid, Bean¹⁶ reported that k_α/k_β was 1.6. These observations suggest that the Brønsted exponent, and

TABLE 2

Activation parameters for trichloroacetic acid catalysis

Exchange	H_2O mole fraction	ΔH^\ddagger ^a (± 2)	ΔS^\ddagger ^b (± 8)	Relative rates of exchange ^c
Pyrrole N-H	0.05	61.7	-92	15
	0.13	63.8	-84	15
Pyrrole $\text{C}_\alpha\text{-H}$	0.18	68.9	-84 ^d	2.7
	0.18	68.5	-92 ^e	1 ^e
Indole $\text{C}_\beta\text{-H}$	0.12	54.2	-122	12
Indole N-H	0.10	<i>f</i>	<i>f</i>	1 000

^a kJ mol^{-1} . ^b Units are $\text{J K}^{-1} \text{ mol}^{-1}$. ^c In 0.10 mole fraction ${}^2\text{H}_2\text{O}$ -acetonitrile containing 0.05M-trichloroacetic acid. ^d Statistically corrected. ^e $k = 1.75 \times 10^{-4} \text{ s}^{-1}$ at 31° . ^f Catalysis by H_3O^+ is significant in the range of solvent composition studied.

hence the extent of hydrogen transfer in the transition state, differs at the α - and β -carbon in pyrrole and differs between the nitrogen sites in indole and pyrrole. Molecular orbital calculations predict a higher π -electron density at C_α due to the electron-withdrawing effect of the nitrogen, but atom localisation energies suggest that it is easier to localise two π -electrons at the α - than at the β -position.^{16,17} Presumably, an electrophilic reagent which gives a transition state with a well developed double bond will be controlled by the localisation energy and preferentially react at C_α , but an electrophilic reagent which gives a transition state having little bond formation is directed preferentially to the β -position by the π -electron density.

Conclusions.—We believe that general acid catalysis has been observed for the three C-H exchange processes and for the N-H exchange in pyrrole; there is little doubt that such a process exists for indole also. We would naturally wish to determine w values for these reactions,¹⁸ as we have for the hydronium ion catalysed exchange reactions.¹ Unfortunately, the acidity functions found in the system ${}^2\text{H}_2\text{O}$ -acetonitrile-trichloroacetic acid were dependent on indicator concentration,⁸ presumably because of ion-pairing effects which cannot be guessed in the cases of partly protonated indole and pyrrole; this therefore cannot be done. For pyrrole N-H exchange, the ${}^2\text{H}_2\text{O}$ mole fraction range 0.02–0.10 can be assumed to represent the region free from significant hydronium ion catalysis. The rate of N-H exchange closely follows the apparent ${}^2\text{H}_0$ acidity

¹⁵ R. P. Bell and P. Jones, *J. Chem. Soc.*, 1953, 88.

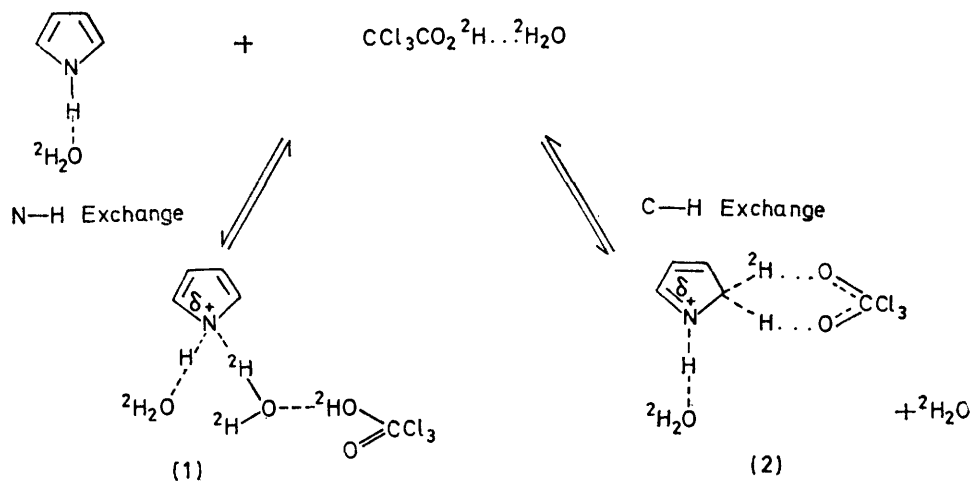
¹⁶ G. P. Bean, *Chem. Comm.*, 1971, 421.

¹⁷ R. D. Brown, *Austral. J. Chem.*, 1955, 8, 100.

¹⁸ J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, 83, 4956.

function but the C-H exchange rates deviate slightly. A first power dependence on $^2\text{H}_2\text{O}$ could rationalise the results of Figure 3, but it is unlikely that proportionality to $[\text{}^2\text{H}_2\text{O}]^2$, as found for hydronium ion catalysis of N-H exchange would be compatible. Transition states (1)

mechanism following protonation at C_α or C_β by the trichloroacetic acid molecule. Bell and Jones¹⁵ have argued that the concerted mechanism is unlikely in aqueous solutions, and we find that N-H and C-H exchange processes are different. Gold¹⁹ suggests that



and (2), which most nearly accord with *a priori* arguments, and which derive support from the entropies of activation cited above, also satisfy the evidence of Figure 3. They would require w values of 0 and 1 for N-H and C-H exchange, if full hydration of both pyrrole and trichloroacetic acid molecules is assumed.

We dismiss the possibility that N-H exchange in indole and pyrrole could take place *via* a concerted

the relative rates of exchange of $[3\text{-}^3\text{H}_1]\text{indole}$ with $^1\text{HOAc}$ and $^2\text{HOAc}$ indicate that the acetate ion is released in the transition state.

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¹⁹ V. Gold, *Discuss. Faraday Soc.*, 1965, **39**, 94.