Electrophilic Substitution in Pyrroles. Part 4.[1] Hydrogen Exchange in Acid Solution

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Hydrogen exchange at the unsubstituted positions in 1,2,5-trimethyl- and 1,3,4-trimethyl-pyrrole in aqueous buffer has been examined. The two positions were found to be of similar reactivities. General acid catalysis was detected. No hydrogen exchange on the methyl groups of 2,3,4,5-tetramethylpyrrole, even in strong acid, was detected. The ^{13}C n.m.r. spectrum of the tetramethylpyrrole was examined.

HYDROGEN exchange is a convenient and much used method for the study of the mechanism of electrophilic aromatic substitution. In this report we describe an investigation into the mechanism of hydrogen exchange of pyrroles in aqueous buffer. There are several problems in the study of this ring system. First, there are three different sites for exchange. We reduced this to one by methylation of one of the ring sites and by *N*-methylation. Secondly, pyrroles polymerise in acid solution.[2] However, this is more pronounced with unsubstituted pyrroles and the compounds used in this study, 1,2,5-trimethyl- and 1,3,4-trimethyl-pyrrole, were carefully chosen and are relatively stable in acid solution. Thirdly, the reaction is very fast and becomes manageable only at high pH.

The matter has been examined by several previous workers. Koizumi and Titani[3] found that in 0.1M-acid all the protons in pyrrole exchange rapidly. Schwetlick *et al.*[4] studied the protiodedeuteriation of [2,3,4,5-^{2}H$_4$]-pyrrole by i.r. spectroscopy and showed that the overall rate of exchange is 10^{15} faster than that for benzene. Bean[5] demonstrated that deuteriodeprotonation of pyrrole and 1-methylpyrrole in aqueous dioxan is general acid catalysed. A similar result was obtained by Muir and Whiting[6] with aqueous acetonitrile as the solvent.

The media we used for a study of the protiodetritiation of two substituted pyrroles were aqueous buffers. Protiodetritiation rates at both the α- and β-positions in a series of phosphate buffers of identical pH were measured as a function of concentration of undissociated acid in the buffer. The results for 1,3,4-trimethyl-2,5-ditritio- and 1,2,5-trimethyl-3,4-ditritio-pyrrole are shown in Figure 1. The linearity of the curves, with positive slope in both cases, proves that general acid catalysis does occur and the second-order rate constants for exchange at the α- and β-positions are 1.4×10^{-2} and 3.3×10^{-3} l mol^{-1} s^{-1}, respectively. It is reasonable to suggest, therefore, that the mechanism of hydrogen exchange is A–S_E2.

In a further series of experiments exchange rates in phosphate buffers of different pH were measured and the results are given in the Table. In a buffer hydrogen exchange may be effected by hydrogen ions (H$^+$) and by undissociated acid (HA) and there may be a spontaneous reaction (k_0). The observed rate constant (k_{obs}) is made up of three terms [equations (1)]. Values of k_{HA}[HA] were computed from the values of k_{HA} given above and (k_{obs} − k_{HA}[HA]) was plotted against [H$^+$] (Figure 2).

$$k_{obs} = k_0 + k_{H^+}[H^+] + k_{HA}[HA] \qquad (1)$$

The curves obtained are linear with a positive slope proving that protiodetritiation is effected by hydrogen ions. The values of k_{H^+} for exchange at the α- and β-positions are 1.9×10^2 and 2.1×10^2 l mol^{-1} s^{-1} respectively. The curve for 1,3,5-trimethylpyrrole passes through the origin and so k_0 for this reaction is either zero or too small to determine in this manner. For 1,2,5-trimethylpyrrole there appears to be a spontaneous reaction, but the error in k_0 is too large to make it worth recording.

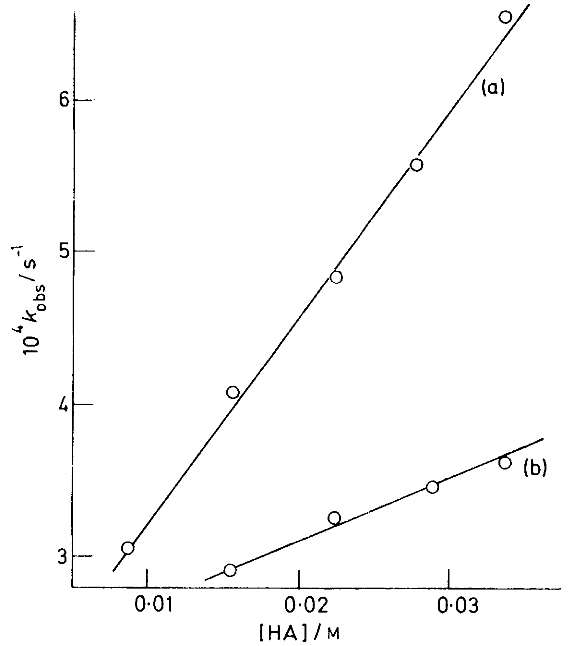


FIGURE 1 Variation of k_{obs} with concentration of undissociated acid for (a) 1,3,5-trimethylpyrrole and (b) 1,2,5-trimethylpyrrole

The rate constants obtained allow us to compare the reactivities of the two ring positions in pyrrole. For the weaker electrophile, *i.e.* undissociated acid, k_α/k_β is 4.0, while for the hydrogen ion the ratio is 0.9. These calculations assume that the activating effect of a methyl group at the α- on the β-position is the same as that of a methyl group at the β- on the α-position. We know of no experimental evidence from the literature to confirm this suggestion. Even in our full study [7] of the effect of methyl groups on the kinetics of the Ehrlich reaction, results for a crucial compound, 2,5-dimethylpyrrole, were unobtainable. However, even if the above assumption is only approximate, the change we observed in the value of k_α/k_β is still real. It is often stated that the α-position in pyrroles is much more reactive in electrophilic substitution reactions than the β-position,[8] but this is not borne out by this study of hydrogen exchange. Previous work on this reaction also does not indicate a substantially more reactive α-position. Schwetlick *et al.*[4] reported a value for k_α/k_β of only 2.5 for hydrogen exchange in methanol–water–sulphuric acid. Muir and Whiting [6] found the ratio to be *ca.* 1 for perchloric acid in aqueous acetonitrile, while Bean [5] reported that, in a medium containing trifluoroacetic acid, exchange at the β-position is faster than at the α-position. The various values quoted for k_α/k_β show that the relative reactivity of the two positions depends markedly upon the medium and the electrophile. Our results suggest that stronger electrophiles are less selective, a conclusion which is in agreement with general principles.

Variation of protiodetritiation rates with pH in aqueous buffer at 25 °

ph	$10^4k_{obs}/s^{-1}$	[HA]/M	$10^4(k_{obs} - k_{HA}[HA])/s^{-1}$
(a) 1,3,4-Trimethyl-2,5-ditritriopyrrole			
5.89	6.09	0.0262	2.35
6.15	4.84	0.0225	1.60
6.33	3.48	0.0188	0.80
6.67	1.98	0.0106	0.47
(b) 1,2,5-Trimethyl-3,4-ditritiopyrrole			
5.20	14.8	0.0330	13.7
5.47	9.42	0.0309	8.39
5.73	6.31	0.0288	5.35
6.16	3.27	0.0225	2.52
6.29	2.54	0.0188	1.91

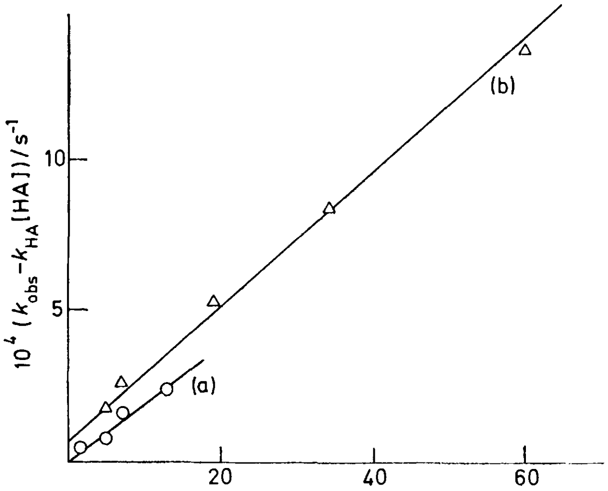
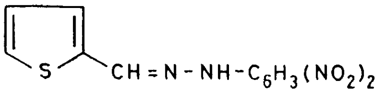


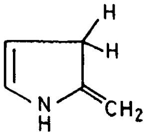
FIGURE 2 Effect of [H+] on hydrogen exchange for (a) 1,3,4-trimethylpyrrole and (b) 1,2,5-trimethylpyrrole

In view of these results it is interesting to see why, in synthetic procedures, α-substituted pyrroles are normally obtained.[9] If the products were kinetically controlled this should not be the case. However, our previous work [10] has shown that electrophilic substitution on pyrroles may be reversible and so the predominant product of reaction is determined by thermodynamic factors. Evidence for this comes from a study of the basicities of the pyrroles used in this study.[11] The pK_a values of 1,2,5-trimethyl- and 1,3,4-trimethylpyrrole are −0.10 and 1.4; from the results obtained in this study there is no obvious correlation between these figures and the rates of protonation. Politzer and Weinstein [12] have produced a theoretical explanation for preferential attack at the α-position, but their conclusions are premature in view of the experimental evidence.

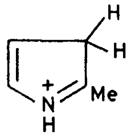
With some methyl-substituted heteroaromatic compounds it is possible to get electrophilic attack on the methyl group as well as on the ring. For example, Tedder *et al.*[13] reported that 2,4-dinitrobenzenediazonium ions react with 2,5-dimethylthiophen to give (1) as one of the products. Also, in acid solution there is hydrogen exchange in the methyl groups of 2-methylthiophen [14] and 2-methylbenzothiophen.[15]



(1)



(2)



(3)

It is possible that attack on a methyl group may be responsible for the reaction between 4-dimethylaminobenzaldehyde and 2,3,4,5-tetramethylpyrrole, although Treibs and Derra-Scherer [16] have suggested that ring attack occurs with loss of methanol. Isolation and characterisation of the product of this reaction is difficult [7] and so we looked for evidence of the susceptibility of the methyl groups to electrophilic attack by a study of hydrogen exchange. The pyrroles studied were dissolved in deuteriotrifluoroacetic acid and ^{1}H n.m.r. spectra taken at timed intervals. An internal standard of dichloromethane was incorporated into the sample, and the integrals of the methyl groups were compared with the standard. Under these experimental conditions any proton attached directly to the ring had exchanged before the first spectrum was run. Over 4 h no change in the spectra of 2,3,4,5-tetramethyl- and 2,5-dimethylpyrrole occured. Therefore, unlike methylthiophens [14] the methyl groups attached to pyrrole do not undergo hydrogen exchange. This is surprising, for formation of species such as (2), which would lead to hydrogen exchange on the methyl group, look plausible. Perhaps the ready location of the positive charge on nitrogen, as in (3), makes loss of a proton from the methyl group energetically unfavourable. These experiments have thrown no light on the nature of the reaction between 4-dimethylaminobenzaldehyde and tetramethylpyrrole.

Tetramethylpyrrole does show anomolous behaviour in a number of other reactions. It is very air sensitive[17] and the methylation of 2,3,4,5-tetramethylpyrrole is reported to give 2,2,3,4,5-pentamethyl-2*H*-pyrrole, rather than *N*-methylation.[18] It is possible that steric crowding of the methyl groups could be the cause of this. It is known that the effect of several substituents on the chemical shifts in the ^{13}C n.m.r. spectra of pyrroles is additive.[19] Steric interactions in tetramethylpyrrole should lead to a breakdown in this additivity. This can be tested by the method of Abraham *et al.*[19]

The shift for the α-carbon atom in unsubstituted pyrrole is 117.3 p.p.m. The calculated effect of methyl groups at positions 2—5 is $+5.4$ $(+10.8 - 2.1 - 2.4 - 0.9)$. Because of 2,3, 4,5, and 3,4 methyl group interactions this is modified by -0.6 $(-0.7 + 0.2 - 0.1)$ and the final calculated shift is 122.1 p.p.m. The observed value is 120.7 p.p.m; the similarity suggests that there is no substantial steric interaction between the methyl groups.

The same calculation can be made for the β-carbon atoms. In unsubstituted pyrrole the shift is 107.6 p.p.m. The effect of the methyl groups at positions 2—5 is $+13.7$ $(-1.2 + 1.1 + 12.7 + 1.1)$. The correction for 2,3, 4,5, and 3,4 methyl group interactions is -6.7 $(-3.8 - 0.1 - 2.8)$, which gives a final value of 114.6 p.p.m. The observed value is 113.8 p.p.m. and again there is no evidence of steric interactions. At present, we have no explanation for the anomolous behaviour of tetramethylpyrrole.

EXPERIMENTAL

Materials.—The *N*-methylation of 2,5-dimethylpyrrole was by the method of Hinman and Theodoropulos.[20] Literature methods were used for the preparation of 1,3,4-trimethyl-[20] and 2,3,4,5-tetramethyl-pyrrole.[21] Deuteriotrifluoroacetic acid was prepared by the reaction of trifluoroacetic anhydride and D_2O.

Tritiation of Pyrroles.—The appropriate pyrrole was added to a mixture of 49% H_2SO_4 (1 ml) and tritiated water (1 ml; 50 mCi ml^{-1}) and stirred for 1 h. The resultant mixture was added to an excess of 0.5M-NaOH and extracted with ether (2 × 50 ml). The ether extracts were washed with water (2 × 50 ml), dried ($MgSO_4$), and the solvent removed by evaporation. The tritiated pyrroles were then distilled.

Kinetic Method.—An aqueous solution of the pyrrole was prepared by addition of one drop of the pyrrole to water (100 ml) and, after stirring, filtration through a phase-separating paper. A portion (10 ml) of this solution was placed in a 50 ml volumetric flask and made up to the mark with phosphate buffer of known composition and pH. The ionic strength was adjusted to 0.53M by addition of KCl. From this solution, kept in a thermostatted water bath at 25 °C, portions (1.0 ml) were removed at timed intervals and run into NaOH solution. This was extracted with toluene-based scintillation cocktail (10 ml) and the organic layer separated, washed with water, and dried ($MgSO_4$). The activity of a portion (5.0 ml) was measured by the use of a Beckman LS100 counter. Spectral studies had shown that extraction of pyrrole from an aqueous solution by toluene was qualitative. The pH of the solution was measured before and after each run by the use of a Beckman Research pH meter with glass and calomel electrodes. The rate constants were calculated by the method of Swinbourne.[22]

As a check that no decomposition or polymerisation of the pyrrole had occurred during the run, a portion (1 ml) of each solution was mixed with 0.25M-4-dimethylaminobenzaldehyde in HCl before and after the run.[11] The absorbances of the resulting coloured solutions were the same, showing that polymerisation and decomposition had not occurred.

N.m.r. Studies.—An approximately equimolar mixture of pyrrole and dichloromethane in $CDCl_3$ was prepared, with tetramethylsilane as an internal reference. The integrals corresponding to the dichloromethane and the methyl groups were measured. Then a number of spectra of the same CH_2Cl_2–pyrrole mixture in CF_3CO_2D were recorded at timed intervals. The relative integrals remained unchanged.

The ^{13}C n.m.r. spectrum of 2,3,4,5-tetramethylpyrrole was recorded with $CDCl_3$ as solvent and tetramethylsilane as internal reference.

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