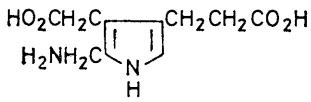
Electrophilic Substitution in Pyrroles. Part I. Reaction with 4-Dimethylaminobenzaldehyde (Ehrlich's Reagent) in Acid Solution

By **Robert S. Alexander** and **Anthony R. Butler,*** Department of Chemistry, The University, St. Andrews, Fife

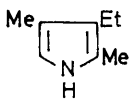
The kinetics of the reaction between various pyrroles and 4-dimethylaminobenzaldehyde (DMAB) in acid solution has been examined by stopped-flow spectrophotometry. The mechanism is rate-determining attack by *O*-protonated DMAB on free pyrrole followed by elimination of water. The activating effect of a methyl group on various positions in the pyrrole ring has been determined.

THERE have been few kinetic or mechanistic studies of electrophilic substitution in pyrroles. The pyrrole ring is very susceptible to electrophilic attack and generally polysubstituted products are formed; even iodination leads to a mixture of mono-, di-, and tri-iodopyrrole.[1] In acid solution some pyrroles undergo polymerisation and this seriously affects many electrophilic substitution reactions.[2] Finally, pyrroles are readily subject to autoxidation to give products of unknown composition.[2] The complexities of the situation are thus apparent.

There is one reaction of pyrroles of considerable importance which appears to be an example of electrophilic attack: it is the reaction with 4-dimethylaminobenzaldehyde (DMAB) in acid to give highly coloured products. This is known as Ehrlich's pyrrole test [3] and is used in the detection of porphobilinogen (I),[4] urobilinogen,[5] and various alkaloids,[6] all matters of considerable clinical importance. The reaction became of further significance when it was found that the urine of individuals suffering from some psychotic illnesses contains cryptopyrrole (II), which is known as the ' mauve factor ' by virtue of its reaction with DMAB.[7] More recently reaction with DMAB has been used in the detection of various hallucinogens.[8] However, the reagent is not a particularly good one for these purposes as the colours fade fairly rapidly [9] and the test cannot be used quantitatively. The present work has two aims: to study the kinetics of electrophilic attack on the pyrrole ring and to develop an improved colourimetric test for pyrroles.



(I)



(II)

EXPERIMENTAL

Materials.—Pyrrole, 1-methylpyrrole, 2,5-dimethylpyrrole, cryptopyrrole, pyrrole-2-carboxylic acid, and indole were obtained commercially. 2-Methyl-,[10] 2,3-dimethyl-,[11] 2,4-dimethyl-,[12] 2,3,5-trimethyl-,[10] and 2,3,4,5-tetramethylpyrrole [13] were prepared by known methods. Preparation of 3,4-dimethylpyrrole by the method of Stapfer and D'Andrea [14] was unsuccessful but the compound was readily obtained by another published route.[10] The *N*-methylated compounds were prepared by reaction of the appropriate methylpyrrole with iodomethane in DMSO.[15] 4-Dimethylaminobenzaldehyde and HCl were AnalaR grade.

Kinetics.—A ' Canterbury ' stopped-flow spectrophotometer was used for most of the kinetic studies. A very dilute solution of pyrrole in water was placed in one arm and DMAB in standard HCl in the other. The oscilloscope trace obtained on mixing was photographed. The wavelengths used for the various pyrroles were as follows (see Table 1): 500 nm, (o); 525 nm, (c)—(e), (i), (l); 535 nm, (a), (f), (g), (k); 560 nm, (b), (h), (j), (n). As constant infinity readings were not obtained in all cases the observed rate constants were calculated by the method of Kezdy [16] and Swinbourne.[17] the slow reaction of pyrrole-2-carboxylic acid was examined by the use of a Unicam SP 500 spectrophotometer. Spectra of the coloured products were recorded on a Unicam SP 800 spectrophotometer but, as the colours faded, the results were not very satisfactory.

Products.—DMAB (1.5 g) Was dissolved in carbon tetrachloride (30 ml) and to this was added water (150 ml) containing concentrated HCl (2 drops) and pyrrole (0.8 g) dissolved in carbon tetrachloride (15 ml). The mixture was refluxed for 3 h, cooled, the water layer separated and washed with ether (3×). The salt was obtained as a dark solid by evaporation of the aqueous solution.

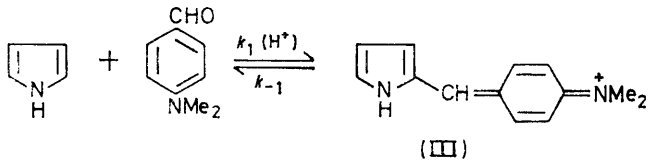
RESULTS AND DISCUSSION

DMAB Reacts with pyrrole according to Scheme 1.[18] Evidence in support of the proposed structure of (III) will be discussed later but its intense colour makes the rate of its formation easy to measure. However, the kinetics of the reaction are far from simple to interpret. Broadly, pyrrole compounds fall into three classes with respect to their reaction with DMAB.

(1) The simplest behaviour is good first-order kinetics (DMAB and acid are present in large excess) with, on a

[1] M. Farnier and P. Fournari, *J. Heterocyclic Chem.*, 1975, **12**, 373.
[2] G. F. Smith, *Adv. Heterocyclic Chem.*, 1963, **2**, 287.
[3] P. Ehrlich, *Medicin Woche*, 1901, 151.
[4] I. D. P. Wootton, ' Microanalysis in Medical Biochemistry,' Churchill Livingstone, Edinburgh, 1974, p. 275.
[5] C. J. Watson and V. Hawkinson, *Amer. J. Clin. Pathology*, 1947, **17**, 108.
[6] H. W. van Urk, *Pharm. Weekblad*, 1929, **66**, 473.
[7] D. G. Irvine, W. Bayne, H. Miyashita, and J. R. Majer, *Nature*, 1969, **224**, 811.
[8] G. V. Alliston, A. F. F. Bartlett, M. J. de Faubert Maunder, and G. F. Phillips, *J. Pharm. Pharmacol.*, 1971, **23**, 72.
[9] Association of Clinical Pathologists, broadsheet 70.
[10] R. L. Hinman and S. Theodropulos, *J. Org. Chem.*, 1963, **28**, 3052.
[11] H. W. Roomi and S. F. MacDonald, *Canad. J. Chem.*, 1970, **48**, 1689.
[12] H. Fischer, ' Organic Syntheses,' 1943, Coll. Vol. II, p. 217.
[13] A. W. Johnson, E. Markham, R. Price, and K. B. Shaw, *J. Chem. Soc.*, 1958, 4254.
[14] C. H. Stapfer and R. W. D'Andrea, *J. Heterocyclic Chem.*, 1970, **7**, 651.
[15] H. Heaney and S. V. Ley, *J.C.S. Perkin I*, 1973, 499.
[16] F. J. Kezdy, J. Jaz, and A. Bruylants, *Bull. Soc. chim. belges*, 1958, **67**, 687.
[17] E. S. Swinbourne, *J. Chem. Soc.*, 1960, 2371.
[18] H. Fischer and H. Orth, ' Die Chemie des Pyrrols,' Akademische Verlagsgesellschaft mbH, Leipzig, 1937, vol. 2.

stopped-flow time scale, a constant infinity reading (Figure 1). This behaviour is shown to a reasonable degree, by compounds (b)—(h) and (j)—(o) (see Table 1).



(III)

SCHEME 1

Over a much longer time (1 h) the colour in most cases faded.

(2) With pyrrole itself first-order kinetics are observed initially but fading commences almost immediately and it is impossible to obtain the infinity reading (Figure 2).

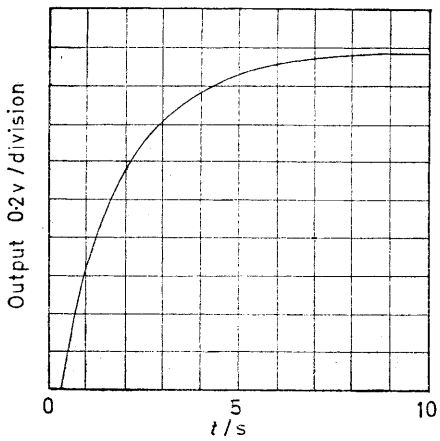


FIGURE 1 Oscilloscope trace for the reaction of DMAB with 1-methylpyrrole in 1.5M-hydrochloric acid: [DMAB] = 0.10M; [1-methylpyrrole]$_0$ = 4 × 10^{-5}M

(3) 2,3,5-Trimethylpyrrole showed the behaviour illustrated in Figure 3. After an increase in absorbance, which may be first order, the colour intensity increased

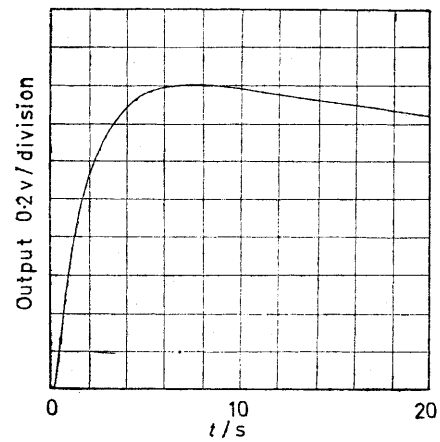


FIGURE 2 Oscilloscope for the reaction of DMAB with pyrrole in 1.5M-hydrochloric acid: [DMAB] = 0.13M; [pyrrole]$_0$ = 3 × 10^{-5}M

in a linear manner over several minutes. After that the colour faded, falling to *ca.* 50% of its maximum value in 1 h. With this compound attack must be at the 3-position, but similar behaviour is not found with (e) and (d).

The general picture that emerges is that an initial reaction, which obeys first-order kinetics, may be followed by further intensification of the colour, and in the

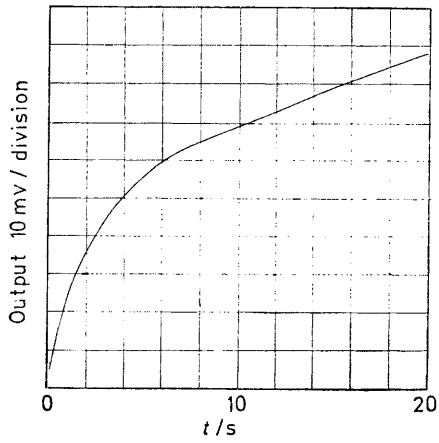


FIGURE 3 Oscilloscope trace for the reaction of DMAB with 2,3,5-trimethylpyrrole in 1.5M-hydrochloric acid: [DMAB] = 0.13M; [2,3,5-trimethylpyrrole]$_0$ = 6 × 10^{-4}M

final phase this fades but does not disappear completely. The relative importance of the three phases varies with the pyrrole and this decides if the initial reaction can be separated and analysed satisfactorily. Fortunately this is the case with most of the pyrroles studied and the only disappointment is that attack at the 3-position could not be analysed satisfactorily.

In all cases the rate of reaction was determined as a function of DMAB concentration at constant acidity. A plot of the experimentally determined rate constant (k_{obs}) against DMAB concentration was linear in all cases, but with some pyrroles there was a large positive intercept. This shows that the equilibrium in Scheme 1 is not completely to the right-hand side and the data fit equation (1).[19] Absence of an intercept indicates that

$$k_{obs} = k_1[\text{DMAB}] + k_{-1} \qquad (1)$$

k_{-1} is zero. The slope of the curve is, of course, k_1 and the results for 3,4-dimethylpyrrole are shown in Figure 4. In four cases examined k_{obs} was found to be independent of the initial pyrrole concentration. The values of k_1 and k_{-1} are listed in Table 1. With compounds (c), (i), and (o) variation of k_{obs} with DMAB concentration was so small that only a very approximate value of k_1 could be determined. For (i), which showed the kinetic behaviour illustrated in Figure 3, calculating a first-order rate constant from the initial part of the curve was an act of faith and little significance can be attached to the value of k_1. All those pyrroles undergoing attack at the 3-position, (c), (d), and (i), have a substantial back reaction, *i.e.* the equilibrium constant k_1/k_{-1}, is small. This is also true for the nonactivated compounds (a) and (o). If the

[19] C. F. Bernasconi and R. G. Bergstrom, *J. Amer. Chem. Soc.*, 1973, **95**, 3603.

pyrrole is activated towards electrophilic attack a higher concentration of product exists at equilibrium, which is what might be expected. The 3-position of pyrrole is less susceptible to electrophilic attack than the 2-position,[20] so the results for (c), (d), and (i) are consistent with this rationalization. The only exception to this behaviour is 3,4-dimethylpyrrole and there is no obvious

TABLE 1

Reactions of various pyrroles and indoles with DMAB in 1.50 M-hydrochloric acid

Pyrrole	k_1[a]/l mol^{-1} s^{-1}	k_{-1}[a]/s^{-1}	pK_a[b]	kK_2	k_{rel}[c]
(a) Parent	1.2 (±0.3)	0.4	−3.8(α)	0.41	0.007
(b) 1-Me	5.0 (±0.3)	0	−2.9(α)	1.7	0.03
(c) 2,5-Me_2	<10	4.5	−0.80(α)		
			−0.71(β)		
(d) 1,2,5-Me_3	43(±4)	3.5	−0.21(α)	40	0.80
			−0.10(β)	49	
(e) 2-Me	17 (±2)	0	−0.21(α)	16	0.3
(f) 1,2-Me_2	16 (±2)	0	0.50(α)	63	1
(g) 3,4-Mo_2	30 (±3)	2.8	0.70 (α)	161	2.6
(h) 2,3-Me_2	3.7 (±0.2)	0	1.5(α)	120	1.9
(i) 2,3,5-Me_3	<1	0.25	2.0(α)		
			0.30(β)		
(j) 1,2,3-Me_3	2.0 (±0.2)	0	2.2(α)	316	5
(k) 2,4-Me_2	2.3 (±0.2)	0	2.6(α)	916	15
(l) 3-Et-2,4-Me_2	0.7 (±0.5)	0	3.5(α)	2 278	36
(m) 2,3,4,5-Me_4	0	0	3.7(α)		
(n) Indole					
Parent			−3.5(α)		
(o) 2-CO_2H	$<10^{-4}$	2.5×10^{-4}			

[a] At 25°. [b] Except where indicated, the basicity of the β-position is much less than that of the α-position. [c] Rate relative to 1,2-dimethylpyrrole.

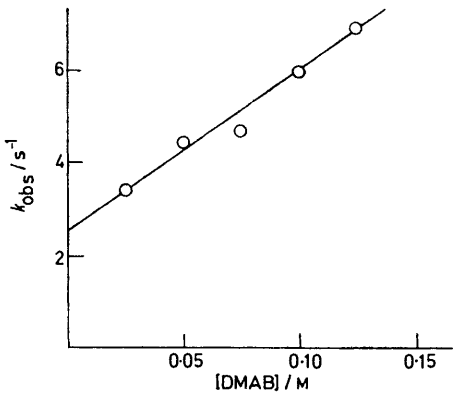
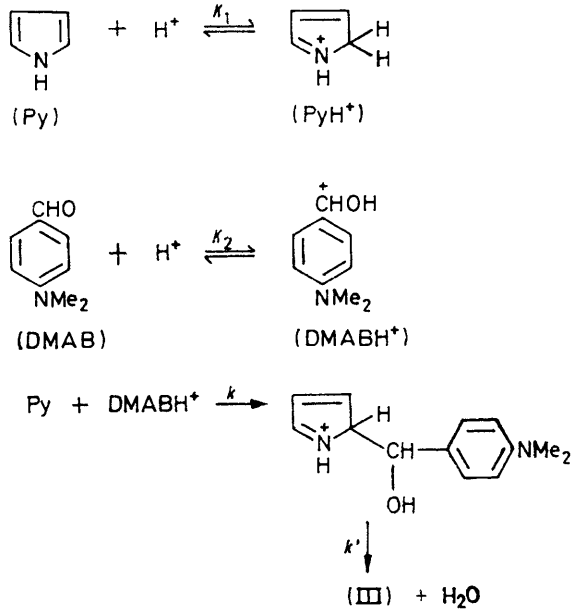


FIGURE 4 Variation of $k_{obs.}$ with DMAB concentration for reaction with 3,4-dimethylpyrrole: [HCl] = 1.5M; [3,4-dimethylpyrrole]$_o$ = 4×10^{-5}M

explanation of this. Indole obeyed good first-order kinetics for each run but a plot of k_{obs} against DMAB concentration showed almost random scatter. A possible reason for this will be given later.

In view of the reaction product and the catalytic effect of acid the reaction mechanism shown in Scheme 2 is proposed. The slow step (k) is attack by *O*-protonated DMAB on unprotonated pyrrole, and elimination of water (k') is fast. The kinetics are made complicated by the fact that pyrroles are protonated to varying extents according to the substitution. K_1 is defined as $[PyH^+]/[Py][H^+]$ and the stoicheiometric concentration of pyrrole, $[Py]_{st}$, is given by equation (2) and the



SCHEME 2

concentration of free pyrrole by (3). K_2 is defined as $[DMABH^+]/[DMAB][H^+]$ and, if the extent of *O*-protonation of DMAB is small, the rate of the slow step is given by (4). As the reaction is of the first order in pyrrole the experimentally determined rate constant, in cases where there is no back reaction, is given by (5) and the rate constant k_1, as defined in Scheme 1, by equation (6). There are four unknowns in this expression and the significant one, that which measures the susceptibility of the pyrrole to electrophilic attack, is k. Determination of the other three will now be considered.

$$[Py]_{st} = [Py](K_1[H^+] + 1) \quad (2)$$

$$[Py] = [Py]_{st}/(K_1[H^+] + 1) \quad (3)$$

$$\text{rate} = k[Py][DMABH^+] = k[Py]_{st}K_2[DMAB][H^+]/(K_1[H^+] + 1) \quad (4)$$

$$k_{obs} = kK_2[DMAB][H^+]/(K_1[H^+] + 1) \quad (5)$$

$$k_1 = kK_2[H^+]/(K_1[H^+] + 1) \quad (6)$$

The equilibrium constant K_1 is related to the pK_a of the pyrrole. At one time pyrrole was thought to be moderately strong base (pK_a = 0) [21] but this was due to an erroneous interpretation of experimental results. More recent n.m.r. studies in strongly acid media have established that *O*-protonation and not *N*-protonation

[20] A. Gossauer, 'Die Chemie der Pyrrole,' Springer-Verlag, Berlin, 1974, p. 105.
[21] N. Naqvi and Q. Fernando, *J. Org. Chem.*, 1960, **25**, 551.

occurs.[22,23] Chiang and Whipple [24] have measured the basicities of a number of substituted pyrroles and values relevant to this study are given in Table 1. K_2 is the equilibrium constant for *O*-protonation of DMAB and is not known, but it is the same in all cases and cancels out in the determination of relative rates. The *N*-protonated compound, which will be the predominant species, is assumed to be unreactive and its presence does not change the form of equation (6). The value of $[H^+]$ in equation (6) is not easy to assess. The acid concentration (1.5M) is outside the ideal range but it is not clear which is the appropriate acidity function to use. The protonation of pyrrole and its methyl derivatives parallels the H_0''' and H_I acidity functions, but log I (where I is the ionization ratio) is also linear with respect to H_0.[24] Protonation of DMAB should parallel the benzophenone scale (H_B) [25] but at low acid concentration H_B and H_0 are identical. The h_0 value [26] is not, therefore, an unreasonable choice and, in any case, the choice has only a small effect on the relative rates.

TABLE 2

Activating effect of a methyl group towards electrophilic attack on the pyrrole ring

Compounds compared	Position of methyl group	Position of attack	Activating effect
(a) and (b)	1	2	4.3
(e) and (f)			3.3
(h) and (i)			2.6
		Mean value	3.4
(a) and (e)	2	5	85
(b) and (f)			67
		Mean value	76
(e) and (k)	3	2	50
(e) and (h)	3	5	6.3

It is now possible to calculate the value of kK_2 for most of the pyrroles studied and the values are listed in Table 1. The ratios of these values gives the relative magnitude of k. The standard was set at unity for 1,2-dimethylpyrrole as this compound gave among the most reproducible kinetics. The spread of rates is *ca.* 5 000 but this spread is normally obscured by the effect of protonation. By comparing the relative reactivities of various pyrroles examined the activating effect of the methyl group on different positions on the ring can be calculated (Table 2). Where two identical positions are open to attack allowance was made for this. The consistency of the results confirms the proposed reaction scheme. The effect of a methyl group is similar to that observed in hydrogen exchange [24] but in the few other reactions studied activation is much weaker.[27] The activating effect of a methyl group on pyrrole is less than on thiophen [28] but so much confusion surrounds the meaning of comparisons of substituent effects in different ring systems [29] that it is unwise to speculate on the significance of this observation. The uncertain values of k_1 for (c) and (i) makes it impossible to compare the reactivities of the α- and β-positions in pyrrole. Compound (d) cannot be used as the effect of 1-substitution on the β-positions is unknown.

The validity of Scheme 2 has been further confirmed by a study of the effect of acid concentration on k_1. If K_1 is very small (*i.e.* the pyrrole is a weak base), then $K_1[H^+]$ is much less than unity, equation (6) simplifies to $k_1 = kK_2[H^+]$, and k_1 should be a linear function of $[H^+]$. For 1-methylpyrrole (where K_1 is small) k_1 increases continuously with increasing acid concentration (Figure 5) but the increase is not linear using any known acidity scale. The reason for this discrepency is not known. When K_1 is large (*i.e.* the pyrrole is a strong base) equation (6) simplifies to $k_1 = kK_2$ and k_1 should be independent of acidity. This was found to be the case for 2,4-dimethylpyrrole (Figure 5). For a pyrrole of intermediate basicity k_1 should increase initially but become constant at high acid concentration. This was observed with 1,2-dimethylpyrrole (Figure 5).

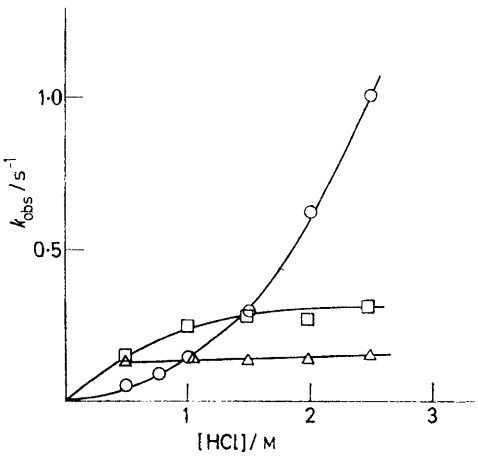


FIGURE 5 Variation of k_{obs} with acid concentration for the reaction of DMAB with various pyrroles: ○, 1-methylpyrrole; △, 2,4-dimethylpyrrole; □, 1,2-dimethylpyrrole

Two other pyrroles examined showed unexpected behaviour. With 1,2,5-trimethylpyrrole there was the expected increase in k_1 at low acidity but above 1M-acid the value decreased (Table 3). The value of k_1 for 2,3-dimethylpyrrole showed a slight but definite decline as the acid concentration was increased (Table 3). Protonation of indoles shows complex behaviour [30] and differently substituted indoles follow different acidity functions. Similar behaviour with pyrroles might explain these effects, but there is no independent evidence for this.

[22] R. J. Abraham, E. Bullock, and S. S. Mitra, *Canad. J. Chem.*, 1959, **37**, 1859.
[23] E. B. Whipple, Y. Chiang, and R. L. Hinman, *J. Amer. Chem. Soc.*, 1963, **85**, 26.
[24] Y. Chiang and E. B. Whipple, *J. Amer. Chem. Soc.*, 1963, **85**, 2763.
[25] T. G. Bonner and J. Phillips, *J. Chem. Soc.* (*B*), 1966, 650.
[26] M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1.
[27] J. Elguero, R. Jacquier, and B. Shimizu, *Bull. Soc. chim. France*, 1969, 2823; H. Rapoport and J. Bordner, *J. Org. Chem.*, 1964, **29**, 2727; J. Meinwald and Y. C. Meinwald, *J. Amer. Chem. Soc.*, 1966, **88**, 1305.
[28] A. R. Butler and J. B. Hendry, *J. Chem. Soc.* (*B*), 1970, 848, 852.
[29] C. D. Johnson and K. Schofield, *J. Amer. Chem. Soc.*, 1973, **95**, 270.
[30] R. L. Hinman and J. Lang, *J. Amer. Chem. Soc.*, 1964, **86**, 3796.

One fact emerged from the ^1H n.m.r. studies: in strong acid at least, proton loss from the pyrrolinium ion is slow. For instance in 16M-deuteriosulphuric acid the half-life of a proton in the 2-position of 1-methylpyrrole is 40 min.[24] Thus, the slow step in electrophilic substitution could be proton loss, followed by a fast reaction between free pyrrole and *O*-protonated DMAB. Very slow proton

TABLE 3

Variation of k_1 with acid concentration for pyrroles (d) and (h)

	k_1/1 mol^{-1} s^{-1}	
[HCl]/M	(d)	(h)
0.15	1.5	
0.40	5.8	
0.50		0.13
1.00	7.2	0.13
1.50		0.12
2.00	4.6	0.096
2.50	3.9	0.077

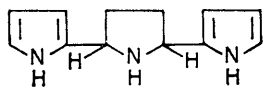
loss occurs only in very concentrated acid and the half-life of β-protonated 2,5-dimethylpyrrole in dilute acid is only a fraction of a second,[23] but this is still the same order of magnitude as the rate of reaction. However, the results in Table 1 argue against proton loss as the slow step. Most of the pyrroles are completely protonated but k_1 varies very little and it is unlikely that the rate of proton loss is unaffected by the large changes in pyrrole basicity. Proton loss does not appear to be the slow step.

Particular interest is attached to the reaction of 2,3,4,5-tetramethylpyrrole as it is claimed by Treibs and Derra-Scherer [31] that it reacts as other pyrroles with DMAB, although no position is unsubstituted. The mechanism proposed [32] involves elimination of methanol, rather than water, in the final step. In the present study it was found that reaction between this pyrrole and DMAB was very slow; with a carefully purified sample the colour took several hours to develop at room temperature. Loss of a methyl group as methanol is an usual process and a more attractive mechanism is protiodemethylation and subsequent reaction of the trimethylpyrrole with DMAB. Tetramethylpyrrole is a strong base and protiodemethylation is not an unlikely reaction. The matter was not investigated further but the fact that a completely substituted pyrrole gives a positive reaction with DMAB does not affect the proposed mechanism in Scheme 2.

A distinctive mechanism for electrophilic substitution in pyrroles has been proposed by Treibs [33] in which a neutral species attacks the protonated pyrrole. Smith [2] has argued convincingly against this mechanism and no support for it comes from the present study. It is highly unlikely that all the basic pyrroles would react at rates which differ so little. However, this is easily understood if reaction is between *free* pyrrole and a positively charged electrophile.

It has been assumed throughout this paper that compounds of the type (III) are the initial products of reaction.[34] Fischer and his co-workers [35] have prepared and identified a number of such compounds but none with only simple alkyl substituents on the pyrrole. The structure of these compounds has been considered in detail by Treibs and Hermann.[36] We prepared a number of products from the pyrroles used in this study; they were deeply coloured solids which proved difficult to purify and identify. These are soluble to only a slight extent in water and insoluble in organic solvents. Elemental analyses were approximately correct for the proposed structure but the mass spectra were difficult to interpret. In dilute acid solution the visible spectra were similar to those obtained under kinetic conditions but, as in both cases the solutions were not stable, complete identification was not possible. The intense absorbance of these compounds is consistent with the long conjugated system of structure (III) and there seems little doubt that this is the correct structure.

The instability of the products must now be considered and polymerization is thought to be an important factor. The more basic pyrroles, which are completely protonated in acid and polymerise only slowly,[37] display fairly straightforward kinetics (see Figure 1). On the other hand, pyrrole itself polymerises in a few seconds in 6M-hydrochloric acid.[38] The product is the trimer (IV),[39] which still has unsubstituted positions on the pyrrole ring and can react with DMAB. This may explain why the colour does not fade completely. The product ob-

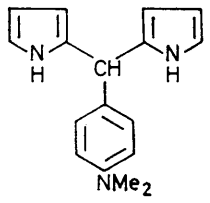


(IV)

tained from the reaction of indole and DMAB contained, from mass spectral evidence, two indolyl groups for each DMAB. Under these conditions then indole probably dimerizes before it reacts.[40] The fact that the kinetics for the reaction of indole and DMAB were impossible to interpret may be the result of this competing reaction. Dimerization and trimerization of indole are known [41] to occur readily in aqueous acid and the resulting solution contains an equilibrium mixture of indole, its dimer, and

[31] A. Treibs and H. Derra-Scherer, *Annalen*, 1954, **589**, 196.
[32] A. Treibs, E. Herrmann, E. Meissner, and A. Kuhn, *Annalen*, 1957, **602**, 163.
[33] A. Treibs, *Angew Chem.*, 1957, **69**, 535.
[34] J. A. Joule and G. F. Smith, 'Heterocyclic Chemistry,' Van Nostrand Reinhold, London, 1972.
[35] H. Fischer and M. Hermann, *Z. physiol. Chem.*, 1923, **122**, 7; H. Fischer and J. Müller, *ibid.*, 1924, **132**, 89; H. Fischer and C. Nenitzescu, *ibid.*, 1925, **145**, 303; H. Fischer and E. Adler, *ibid.*, 1931, **197**, 237.
[36] A. Treibs and E. Herrmann, *Z. physiol. Chem.*, 1955, **299**, 171.
[37] O. Piloty and J. Stock, *Ber.*, 1913, **46**, 1010; H. Fischer and J. Klarer, *Annalen*, 1926, **450**, 199.
[38] W. Tschelinzew, B. Tronow, and B. Woskressenski, *Chem. Z.*, 1916, **87**, 1246; M. Dennstedt and F. Voigtlander, *Ber.*, 1894, **27**, 478.
[39] A. Pieroni and A. Moggi, *Gazzetta*, 1923, **53**, 120; H. A. Potts and G. F. Smith, *J. Chem. Soc.*, 1957, 4018.
[40] H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 1957, 3544.
[41] B. Oddo, *Gazzetta*, 1913, **43**, 385; M. Scholtz, *Ber.*, 1913, **46**, 1082.

trimer, and their salts.[42] Further analysis of the situation is too daunting to contemplate. 2-Methylpyrrole dimerizes in acid solution [43] but pyrroles with both the 2- and the 5-positions substituted do not polymerize.[44] However, the reaction in aqueous solution has not been studied. Therefore, we cannot offer any explanation of



(V)

the strange behaviour illustrated in Figure 3. Cryptopyrrole will dimerize under acid conditions,[45] but the structure of the dimer is unknown. The reaction of this compound with DMAB did not obey good first-order kinetics. Treibs and Herrmann [36] have suggested that formation of a dipyrrylphenylmethane (V) may account for fading of the colour but this seems unlikely under our experimental conditions as DMAB is present in a large excess.

Electrophilic substitution of pyrrole is clearly a complex matter because of the basicity of pyrrole and competing reactions, but this study has provided quantitative, if not accurate, data on the activating effect of methyl groups on the pyrrole ring in one such reaction. The development of improved reagents for the detection and estimation of pyrroles will be described in a future publication.

We thank Dr. K. Smith for advice and P. Pogorzelec for providing samples of several pyrroles. The stopped-flow equipment was purchased with a grant from the S.R.C. and R.S.A. thanks the S.R.C. for a studentship.

[5/1845 *Received*, 24*th September*, 1975]

[42] O. Schmitz-DuMont, B. Nicolojannis, E. Schnorrenberg, and H. H. Saenger, *J. prakt. Chem.*, 1931, **131**, 146.
[43] M. Dennstedt and J. Zimmermann, *Ber.*, 1888, **21**, 3429; P. N. Edwards, M. Sc. Thesis, University of Manchester, 1958.
[44] H. Fischer and B. Walach, *Annalen*, 1926, **450**, 129; H. Fischer, E. Sturm, and H. Friedrich, *ibid.*, 1928, **461**, 249.
[45] H. Fischer, *Ber.*, 1915, **48**, 404.