Observation of an Amplified Isotope Effect during Chlorination of 1-Methylpyrrole. Evidence for Rate Determining Deprotonation of the σ-Complex

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Observation of an amplified isotope effect to the value of 19.10 indicated that there were two kinetically significant proton transfers and deprotonation of the σ-complex was the rate determining step.

Recently[1,2] we reported that 1-methylpyrrole undergoes σ-substitution (addition–elimination) with *N*-chloroacetanilide[1a] and *N*-chloroimides[1b,2] and a nitrogen containing moiety is incorporated into the pyrrole ring. It was proposed that a 2-chloro group makes the pyrrole ring more dienic in character.[1] This is reflected in the transition states leading from the σ-complex to chloropyrroles (deprotonation) and ion-pair collapse (addition). In essence a 2-chloro substituent slows proton transfer and makes ion-pair collapse a competitive process.

These results suggested the possibility that proton transfer might be the rate determining step in the above reactions. To test this possibility the acid catalysed chlorination of 1-methylpyrrole with *N*-chlorobenzamide (NCB) was studied. In this system the same σ-complex would be expected to be formed as in the above studies, but no σ-substitution reaction occurs.[2]

Reaction of equimolar amounts of 1-methylpyrrole (**1**), *N*-chlorobenzamide (NCB) and dichloroacetic acid (DCA) in $CHCl_3$ at 40 °C, under nitrogen, was found by gas chromatography to give after 55 min a mixture of (**1**) (14%), 2-chloro-1-methylpyrrole (71%), 3-chloro-1-methylpyrrole (2%), and 2,5-dichloro-1-methylpyrrole (13%) (Scheme 1). Benzamide was recovered in 96% yield. In the absence of acid and under nitrogen, no reaction[2] between (**1**) and NCB was detected after 48 h. *N*-Chlorobenzamide was completely decomposed after 10—30 min in the presence of HCl at 40 °C, but with DCA only a <3% change was noted after 50 h under nitrogen.[2] No evidence for the formation of an acetyl hypochlorite was detected.[3]

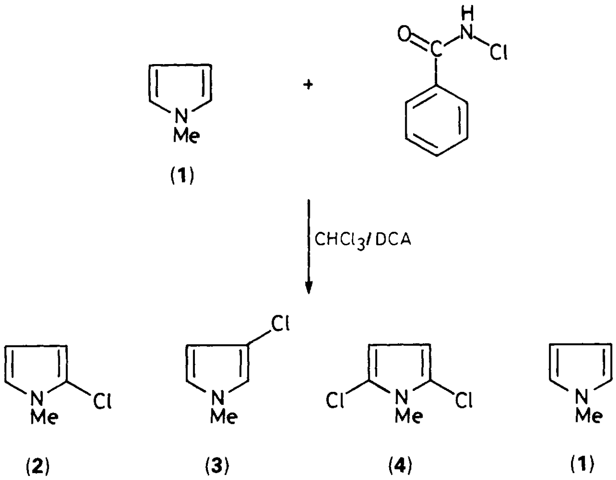
The reaction was followed iodometrically at 40 °C and a pseudo-first-order plot of log V *vs.* t was obtained (k_{obs}) for 98% disappearance of NCB ($r \geqslant 0.995$). The reaction was found to be first-order with respect to 1-methylpyrrole (**1**), NCB and DCA: $k_{obs.} = k^3\,[\mathrm{DCA}][(\mathbf{1})]$ and $k^3 = 1.00 \times 10^{-2}$ $l^2\ mol^{-2}\ s^{-1}$. A linear Arrhenius plot (six points) was obtained, with $\Delta H^\circ = 47.2\ \mathrm{kJ\ mol^{-1}}$, $\Delta S^\circ = -0.133\ \mathrm{kJ\ mol^{-1}}$ and $\Delta G^\circ = 88.8\ \mathrm{kJ\ mol^{-1}}$ at 40 °C.

A primary isotope effect should be observed if deprotonation of (**1a**) is the rate determining step.[4] Under the reaction conditions, 2,5-dideuterio-1-methylpyrrole-methylpyrrole[5] underwent fast H/D exchange with the catalysing acid (HA). Therefore the reaction was carried out with $MeCO_2D$ as the catalyst and $(k^3)_D = 1.55 \times 10^{-5}\ l^2\ mol^{-2}\ s^{-1}$. This can be compared to a value of $2.96 \times 10^{-4}\ l^2\ mol^{-2}\ s^{-1}$ when undeuteriated reagents were used. An amplified[6] isotope effect $[(k^3)_H/(k^3)_D]$ of 19.10 ± 0.19 was observed at 40 °C. From Scheme 2 it can be seen that if the small secondary isotope effect in the chlorine transfer step is discounted, equation (1) applies.

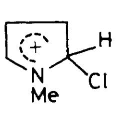
$$(k^3)_H/(k^3)_D = (K_H/K_D)[(k_2)/_H/(k_2)_D] \qquad (1)$$

The equilibrium isotope effect (K_H/K_D) was evaluated from a study of the effect of the pK_a of the catalysing acid on the rate k^3. Plotting $-\mathrm{p}K_a$ *vs.* $\log k^3$ gave a straight line (6 aliphatic acids, $r = 0.98$). From the pK_a of $MeCO_2D$[7] a value of $\log k^3$ was obtained which reflected only the equilibrium isotope effect and K_H/K_D was found to be 3.68. From this value the primary kinetic isotope effect $[(k_2)_H/(k_2)_D]$ was calculated to be 5.19 ± 0.19.

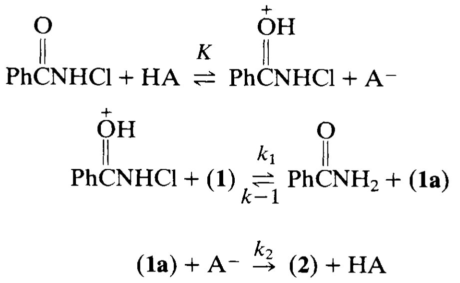
These results demonstrate that deprotonation of σ-complex (**1a**) is the rate determining step in the acid-catalysed chlorination of (**1**) and support the idea that a 2-chloro substituent slows proton transfer.[1a] The results do not rule out the possibility that (**1a**) is particularly stable. This is the first example of rate determining proton transfer during electrophilic substitution in pyrroles. An interesting consequence of this is that the chlorination, and by analogy, halogenation of



Scheme 1



(**1a**)



$$\mathrm{Ph}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{NHCl} + \mathrm{HA} \overset{K}{\rightleftharpoons} \mathrm{Ph}\overset{\overset{+}{\mathrm{O}}\mathrm{H}}{\overset{\|}{\mathrm{C}}}\mathrm{NHCl} + \mathrm{A}^-$$

$$\mathrm{Ph}\overset{\overset{+}{\mathrm{O}}\mathrm{H}}{\overset{\|}{\mathrm{C}}}\mathrm{NHCl} + (\mathbf{1}) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Ph}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{NH_2} + (\mathbf{1a})$$

$$(\mathbf{1a}) + \mathrm{A}^- \xrightarrow{k_2} (\mathbf{2}) + \mathrm{HA}$$

Scheme 2

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pyrroles should be reversible (Scheme 2). This would seem to be supported by the reported instability of 2-chloropyrrole[8] in acid and the acid catalysed rearrangement and debromination of 2-bromopyrrole.[9]

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