Reactivity of a Tetrahedral Intermediate in Hydrolysis of *N*-Acetylpyrrole

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Base hydrolysis of *N*-acetylpyrrole (**1a**) involves formation of an anionic tetrahedral intermediate (**2a**). The equilibrium constant between these two species can be estimated by extrapolation based on the equilibrium constants for hydration of *N*-trichloroacetyl- and *N*-trifluoroacetylpyrrole and the estimated pK_a for deprotonation of the hydrates of these compounds. Inductive effects upon hydration and deprotonation of the hydrates were estimated by analogy with inductive effects upon the equilibrium reactions of chloral and acetaldehyde. The free energies of activation for formation and return of **2a** are approximately 16 and 12.5 Kcal mole^{-1} respectively and for conversion of **2a** to products 11 Kcal mole^{-1} in aqueous 1*M* OH^-.

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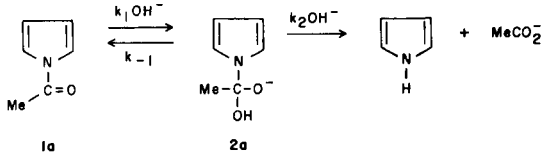
The two stage mechanism of the base hydrolysis of activated amides such as acylpyrroles, indoles and carbazoles is well established and consistently the order with respect to OH^- changes from two to one with an increase in $[OH^-]$ [1,2]. The reaction steps are shown in Scheme 1 for hydrolysis of *N*-acetylpyrrole (**1a**).

Scheme 1



1a 2a

The observed first order rate constant, k_ψ is given by:

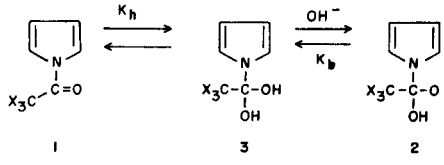
$$k_\psi = k_1k_2[OH^-]^2/(k_{-1} + k_2[OH^-]) \quad (1)$$

and when $k_{-1} \gg \mathbf{k_2}[OH^-]$ the reaction is second order with respect to OH^-, but with increasing $[OH^-]$ the reaction becomes first order with respect to OH^- and $k_\psi = k_1[OH^-]$.

Conversion of the intermediate into products involves deprotonation and C-N bond breaking. These steps may be concerted and a general base is sometimes involved, however for base hydrolysis of *N*-acylpyrrole, OH^- is the effective base. The variation of k_ψ with $[OH^-]$ allows calculation of k_1 and k_{-1}/k_2, and our aim was to separate the rate constants and estimate k_{-1} and k_2. Our approach is to calculate the equilibrium constant for conversion of **1a** into **2a** based on the reactions in Scheme 2.

The equilibrium constant k_1/k_{-1} is given by K_h/K_b. The value of K_a (or K_b) for deprotonation of **3a** can be estimated by comparison of known acidities of *gem*-diols. For deprotonation of the hydrate of α,α,α-trifluoroacetophenone (**4**) $pK_a = 10$ [3]. So far as we know electronic substituent parameters are not available for an *N*-pyrrole group,

Scheme 2

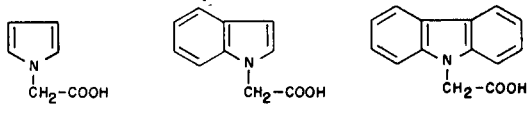


1 3 2

a, X = H
b, X = F
c, X = Cl

but strengths of various carboxylic acids should allow comparison of the inductive effect of *N*-pyrrole and phenyl groups.

Phenylacetic acid, $pK_a = 4.30$ [4] is weaker than the corresponding *N*-azole acetic acids [5-7] for which pK_a values are 3.30, 3.40 and 3.55 respectively.



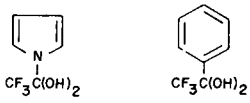
5 6 7

These differences suggest that the *N*-pyrrole group has a larger electron withdrawing effect than phenyl corresponding to approximately one order of magnitude in K_a. Steric effects are probably not very important because pK_a values are similar for **5**, **6** and **7**.

We assume therefore that the pK_a for the hydrate **3b** will have a value approximately one unit more negative than that of **4**, *i.e.*, $pK_a \sim 9$ for deprotonation of **3b**.

The difference between pK_a of **3b** and **4** is probably slightly larger than our estimate because we do not take into account attenuation of inductive effects by the methylene group of phenylacetic acid and **5**, **6** and **7**.

Trifluoromethyl and trichloromethyl groups have similar inductive effects [5], and for the hydrates of chloral and



3b 4

acetaldehyde pK_a values are 10.04 and 13.57 respectively [6], so that pK_a for deprotonation of **3b, 3c** should be approximately 3.5 units more positive than for deprotonation of **3a**, *i.e.*, for **3a** $K_a \sim 2.9 \times 10^{-13}$ and $K_b \sim 0.035$.

It remains to estimate the (hypothetical) equilibrium constant, K_h, for *N*-acetylpyrrole (Scheme 2). For *N*-trichloro- and *N*-trifluoroacetylpyrrole, (**1b, 1c**) values of K_h are 1.2 and 2.5 respectively at 25° [7]. For chloral and acetaldehyde the corresponding values are 2.8×10^4 and 1.5 respectively [6]. Therefore assuming that electronic effects are similar for hydration of aldehydes and *N*-acylpyrroles, $K_h \sim 6.5 \times 10^{-5}$ for *N*-acetylpyrrole (**1a**).

These comparisons give an overall equilibrium constant of $K_h/K_b \sim 1.9 \times 10^{-3} M^{-1}$ for conversion of *N*-acetylpyrrole into the anionic tetrahedral intermediate (Scheme 2) so that for this reaction $\Delta G° \sim 3.7$ kcal mole^{-1}.

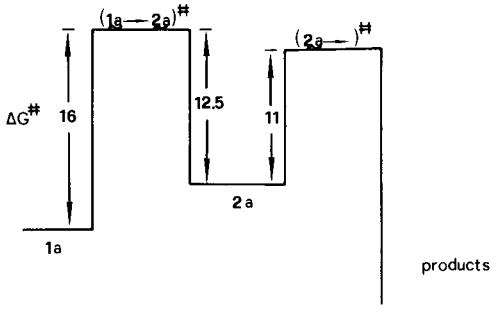


Figure 1. Free energy diagram for base hydrolysis of *N*-acetylpyrrole.

The second order rate constant $k_1 = 8.5\ M^{-1}s^{-1}$ for *N*-acetylpyrrole [8], so that $\Delta G^{\#} \sim 16.2$ kcal mole^{-1} for this reaction, and the first order rate constant for return of **2a** to *N*-acetylpyrrole is $4.5 \times 10^3 s^{-1}$, and $\Delta G^{\#}$ for this reverse reaction is 12.5 kcal mole^{-1}.

Analysis of the variation of k_ψ with [OH$^-$] for base hydrolysis of *N*-acetylpyrrole gives $k_2/k_{-1} = 17.4\ M^{-1}$, so that $k_2 \sim 8 \times 10^4 M^{-1}s^{-1}$ and $\Delta G^{\#} \sim 11$ kcal mole^{-1} for conversion of **2a** into products. These rate constants and free energies of activation or reaction are subject to considerable uncertainty because of the estimation of K_h and K_b by comparison with substituent effect upon hydration of aldehydes and deprotonation of their hydrates and the fact that we are not considering steric or ionic strength effects upon the reactions discussed here. However, they suggest that the base hydrolysis of *N*-acetylpyrrole, and related activated amines, involves formation of an anionic tetrahedral intermediate which has a lifetime much larger than that of an intermediate whose breakdown is diffusion controlled. The free energy diagram is shown in Figure 1 for the hypothetical reaction in 1*M* OH$^-$.

EXPERIMENTAL

Materials.

The substituted acetic acids were prepared from the sodium salts of pyrrole, indole and carbazole by treatment with methyl or ethyl chloroacetate in DMF. The pyrrole derivative was purified by vacuum distillation and the indole and carbazole by recrystallization. The esters were saponified using stirred 2*M* sodium hydroxide at 45° for 12 hours and were isolated by acidification (hydrochloric acid).

The *N*-pyrrolylacetic acid, recrystallized from ligroin had mp 91-92°, lit 91° [9]; nmr (deuterioacetone): δ 4.72 (2H, s, CH_2), 6 (2H, m, β-H), 6.70 (2H, m, α-H), 10.20 (1H, s, OH).

N-Indolylacetic acid, recrystallized from ether-hexane, had mp 175-176°, lit 174-175° [10]; nmr (deuterioacetone): δ 5.02 (2H, s, CH_2), 6.48 (1H, d, 3H), 7.15 (1H, d, 2-H), 7.17 (3H, m, Ar-H), 7.56 (1H, m, 7H).

N-Carbazolylacetic acid after washing well with water and drying had mp 193-194°; nmr (deuterioacetone): δ 5.27 (2H, s, CH_2), 7.37 (6H, m, Ar-H), 8.15 (2H, m, 4,5-H), 9.30 (1H, broad-OH).

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.35; H, 4.98; N, 6.15.

All compounds gave parent peak in the mass spectra at 70 eV.

Dissociation Constants.

The determination of the pK_a was carried out in aqueous ethanol (50% by volume) at 25.0° by titration following standard methods [11]. Albert and Serjeant [11] have shown that the pK_a values for acids similar to those used here are more negative by one unit in water than in ethanol (50%, by volume) and we made this correction.

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