DIRECT MEASUREMENT OF THE RELATIVE RATES OF C-PROTONATION AT UNSUBSTITUTED AND SUBSTITUTED α- AND/OR β-POSITIONS OF A PYRROLE RING

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Direct kinetic measurements of the C-protonation rates of 1,2,5-trimethyl- and 3,4-dimethyl-pyrroles allow the first comparison of the relative kinetic proton affinities of unsubstituted and substituted positions of the pyrrole ring.

INTRODUCTION

C-Protonation of aromatics and heteroaromatics represents the prototype reaction for the addition step of electrophilic aromatic substitutions, but direct kinetic measurements of this process are generally inaccessible, even with highly activated compounds such as 1,3,5-trimethoxybenzene.[1–4] Because these systems are characterized by very low pK_a values and very small kinetic proton affinities, the first-order reverse rates for deprotonation of the conjugate benzenonium and related heteroaromatic cations are extremely high, rendering the observed overall protonation rates in solution out of range of kinetic techniques such as stopped-flow and T-jump. It is only with the highly basic azulenes such as guaiazulene that some direct kinetic-studies of protonation have been successful.[5–7]

To gain some information on these processes, workers have turned their attention to isotopic exchange (detritiation) experiments.[1,8–15] However, this indirect method has two drawbacks: it can provide information only on C-protonation rates at an unsubstituted carbon, and the equation giving the exchange rate contains terms from different isotope effects which so far are subject to various uncertainties.[1–4]
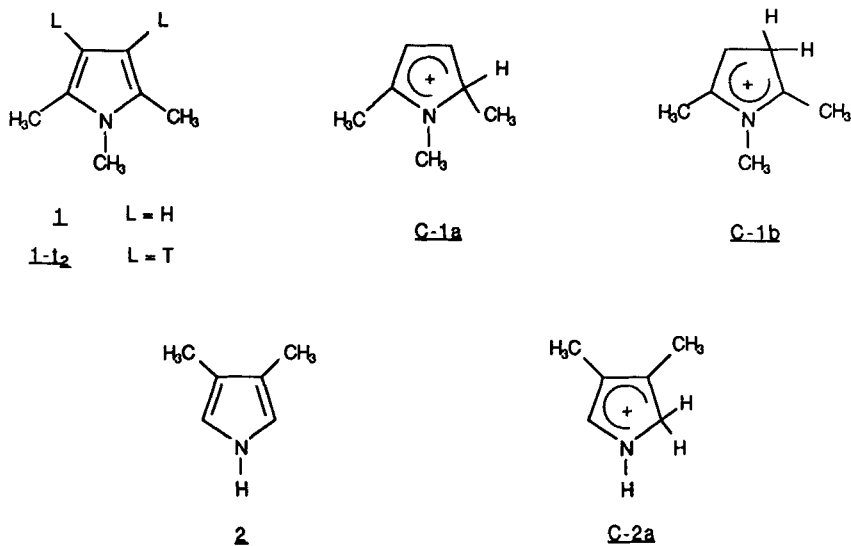
In the indole and pyrrole series, the first direct measurement of a C-protonation rate was made fairly

recently[16] using one of the most basic pyrroles known, 2,4-dimethyl-3-ethylpyrrole (kryptopyrrole). However, protonation of this pyrrole takes place only at an unsubstituted α-carbon and, again, no direct information could be obtained on the relative proton affinities of α- and β-unsubstituted positions.

This kinetic study of the similarly basic pyrroles 1,2,5-trimethylpyrrole (1) and 3,4-dimethylpyrrole (2) largely fills this gap. Thus, the interesting finding has been made that the thermodynamically favoured protonation at a CH_3-bearing α-carbon occurs at a much lower rate than protonation at an unsubstituted α-carbon. In addition, reliable information on the relative proton affinities of α- and β-unsubstituted carbons has been obtained.

RESULTS AND DISCUSSION

Rates of protonation of 1 and 2 in hydrochloric acid solutions (0·05–0·5 M) were determined at 25 °C by a stopped-flow method. Pseudo-first-order conditions with the pyrrole as the minor component were used throughout. The ionic strength was kept constant at 0·5 M with KCl. Under these experimental conditions, only one kinetic process associated with equilibrium formation of the adduct C-1a or C-2a according to equation (1) was observed. In particular, no evidence

$$\underline{1} \qquad L = H$$
$$\underline{1\text{-}t_2} \qquad L = T$$

$$\underline{C\text{-}1a} \qquad\qquad \underline{C\text{-}1b}$$

$$\underline{2} \qquad\qquad\qquad \underline{C\text{-}2a}$$

for initial formation of the isomeric adduct C-1b was found by stopped-flow spectrophotometry. This result is consistent with previous NMR observations that C-1b is thermodynamically less stable than C-1a.[17,18]
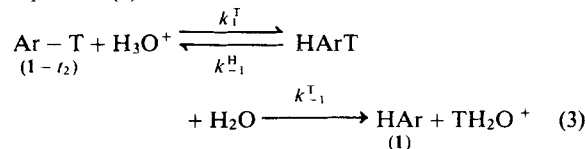
The rate constants k_1^H (statistically uncorrected) and k_{-1}^H for protonation of 1 and 2 by H_3O^+, and deprotonation of C-1a and C-2a by solvent, were readily obtained from plots of the observed first-order rate constant, k_{obsd} vs $[H^+]$, which were linear [equation (2)]. It is noted that the high degree of linearity of these plots provides further evidence for the absence of a competing formation of C-1b under our experimental conditions. From the k_1^H and k_{-1}^H values, statistically uncorrected pK_a values of $0\cdot73$ and $0\cdot90$ can be calculated at an ionic strength of $0\cdot5$ M for C-α protonation of 1 and 2, respectively (see Table 1). (The measured pK_a for C-α protonation of 1 is $0\cdot9$ units higher than that derived previously using the acidity function method in concentrated sulphuric acid solutions,[17] whereas the pK_a for C-α protonation of 2 is consistent

with an earlier determination.[18] The discrepancy in the values for 1 is not understood at present). The k_1^H and pK_a values are statistically uncorrected because the same statistical factor of 2 is included in all protonation processes considered here.

$$1 \text{ or } (2) + H_3O^+ \underset{k_{-1}^H}{\overset{k_1^H}{\rightleftharpoons}} C\text{-}1a \text{ (or } C\text{-}2a) + H_2O \quad (1)$$
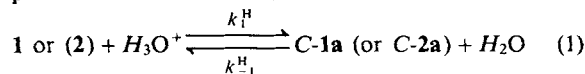
$$k_{obsd} = k_1^H[H_3O^+] + k_{-1}^H \quad (2)$$

An estimate of the rate constant k_1^H for C-protonation of 1 at the β-position to give C-1b has been obtained as follows. The protiodetritiation of 1-t_2 was studied kinetically in dilute HCl solutions $(3 \times 10^{-5}$–$2\cdot4 \times 10^{-4}$ M, no added KCl) where neither adducts C-1a nor C-1b form in appreciable amounts. Accordingly, the first-order rate constant k_{obsd} for the exchange process of equation (3) was simply given by equation (4).[16]

$$\underset{(1-t_2)}{Ar - T} + H_3O^+ \underset{k_{-1}^H}{\overset{k_1^T}{\rightleftharpoons}} HArT$$

$$\underset{(1)}{} + H_2O \xrightarrow{k_{-1}^T} HAr + TH_2O^+ \quad (3)$$

$$k_{obsd} = \frac{k_1^T}{1 + \dfrac{k_{-1}^H}{k_{-1}^T}}[H_3O^+] = k_{exch}[H_3O^+] \quad (4)$$

From the linear dependence of k_{osbd} on the H^+ concentration, a k_{exch} value of $52\,1\,mol^{-1}\,s^{-1}$ at $25\,^\circ C$ was derived. If one assumes a reasonable value of 18 for the k_{-1}^H/k_{-1}^T ratio,[2,3,5-7,16,19] then a statistically uncor-

Table 1. Rate constants and pK_a values for C-α and/or C-β protonation of 1 and 2

Parameter	1		2
	C-α	C-β	C-α
k_1^H (l $mol^{-1}\,s^{-1}$)	27	940	596
k_{-1}^H (s^{-1})	5	—	75
pK_a	$0\cdot73$	$-0\cdot49^a$	$0\cdot90$
	$-0\cdot24^a$		$0\cdot66^b$

[a] Ref. 17.
[b] Ref. 18.

rected k_1^T value of 940 $l\,mol^{-1}\,s^{-1}$ is obtained for protonation at the tritium-labelled β-position of $1 - t_2$. [Our k_1^T value is notably lower than that previously derived from measurements in phosphate buffers ($k_{exch} = 190\,l\,mol^{-1}\,s^{-1}$).[12] Although the reasons for this discrepancy which arises from a different k_{exch} value are also not understood, these respective values would lead to the same overall conclusions in our discussion.] Since isotopic substitution is known to affect only slightly the rate of protonation.[1,16,19] this value can be safely used as a reference for the rate of protonation at the unlabelled β-position of **1**.

Two essential points in the context of electrophilic aromatic substitution emerge from the above results:

(i) Protonation at the hydrogen-bearing C-α carbon of **2** occurs at a much higher rate than protonation at the methyl-α-carbon of **1**. Since both compounds have similar C-α basicities ($\Delta pK = 0\cdot17$), this result shows unequivocally that, other things being equal, electrophilic attack at an unsubstituted ring carbon is kinetically favoured over electrophilic attack at a methyl-substituted ring carbon. This situation is reminiscent of that found in the formation of anionic α-adducts which are the counterpart of the cationic α-adducts in nucleophilic aromatic substitutions.[20,21]

(ii) Protonation at the unsubstituted C-β position of **1** occurs faster than at the unsubstituted C-α position of **2** ($k_1^1/k_2^1 = 0\cdot5$). Noting that the thermodynamic affinity for C-β protonation of **1** is appreciably lower than that for C-α protonation of **2** the observed k_1^1/k_1^2 ratio will represent a minimum value. Hence previous suggestions that the α-position in pyrroles is not necessarily much more reactive than the β-position are confirmed.[12] In fact, exchange experiments have shown that the relative reactivities of the α- and β-positions of a pyrrole ring depend markedly on the medium and the electrophile, with strong electrophiles being less selective.[8,10,22]

EXPERIMENTAL

1,2,5-Trimethylpyrrole (**1**) and 3,4-dimethylpyrrole (**2**) were commercially available samples which were purified by distillation under vaccuum prior to use. $1 - t_2$ was prepared by the general procedure previously described[23] with the modification that an acid catalyst (ca 1 μl of 1 M HCl) was used. The position and extent of tritiation (ca 1 mCi mmol^{-1}) were determined by ^{3}H NMR spectroscopy; only the β-position of the pyrrole ring was found to be labelled.

The kinetics of detritiation were followed by the published procedure[23] using an acid catalyst and with-drawing at regular time intervals 5-ml aliquots of the reaction solution, which was quenched with sodium hydrogencarbonate solution. Kinetic runs were performed in triplicate. Stopped-flow kinetics were performed according to the method used previously.[16]

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