Acid-catalysed Proton Exchange on Pyrrole and N-Methylpyrrole

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Summary Rate constants for the acetic acid-catalysed proton exchange at position-2 and -3 of pyrrole and N-methylpyrrole have been determined and the relative reactivities found to be reversed in dilute trifluoroacetic acid solution.

WE have begun a study of the kinetics of proton exchange on pyrrole and substituted pyrroles using n.m.r. to follow the rate of exchange. At the probe temperatures of 36 °C, exchange in a dioxan–deuterium oxide solution (1 : 1 by weight) to which varying amounts of deuterioacetic acid have been added, can be followed conveniently. For a system containing 10% (by weight) deuterioacetic acid, the observed pseudo-first order rate constants for exchange on pyrrole were: at position-2, 0.0027 min^{-1}; at position-3, 0.0017. In the same medium, the rates of exchange on N-methylpyrrole were 0.0060 and 0.0029 at position-2 and -3, respectively. Thus, under these conditions position-2 of pyrrole is 1.6 times more reactive than position-3. Introduction of the N-methyl group should increase the reactivity, and indeed the reactivity at position-2 is increased by a factor of 2.2, although at position-3, there is only an increase by a factor of 1.3. This is in contrast to the results of nitration where introduction of the N-methyl group increases the amount of 3-substitution, apparently due to the steric effects of the methyl group on nitration at position-2.[1]

In dilute acid solution, proton exchange on reactive aromatic substrates such as trimethoxybenzene and 2-methylindole has been shown to occur *via* the A-S_E2 (general acid-catalysed) mechanism.[2] It is, therefore, not unexpected that a change in the concentration of deuterioacetic acid has a pronounced effect on the rate of proton exchange on pyrrole, although indicator measurements showed that the hydrogen-ion activity (*ca.* $10^{-3.5}$) in such mixed solvent systems remains essentially constant. When deuteriotrifluoroacetic acid (1%) was used as catalyst, the rate of exchange (*ca.* 0.1 min^{-1}) was too rapid to measure accurately, but it was obvious that exchange was occurring slightly faster at position-3. In their study of the protonation behaviour of pyrroles, Whipple, Chiang, and Hinman[3] observed that protonation of N-methylpyrrole in concentrated sulphuric acid is faster at position-3, although the 2-protonated conjugate acid is thermodynamically more stable. In weakly acidic solutions, however, they noted that exchange is faster at position-2. This suggests that with increasing acidity, the transition state is earlier and thus resembles the neutral pyrrole molecule rather than its conjugate acid. M.O. calculations at various levels of sophistication tend to predict a higher π-electron density at position-3 due to the electron-withdrawing effect of the electronegative nitrogen. In contrast, localization energies calculated for the conjugate acid intermediates which would be applicable for a late transition state predict a greater stability for the 2-pyrrolyl conjugate acid.[4]

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[4] M. Scholz and D. Heidrich, *Monatsh.*, 1967, 98, 254, 264; W. H. Adam, A. Grimision, and G. Rodriguez, *Tetrahedron*, 1967, 23, 2513; D. T. Clark, *ibid.*, 1968, 24, 4688; E. Clementi, H. Clementi, and D. R. Davis, *J. Chem. Phys.*, 1967, 46, 47; and unpublished calculations by the author using the "Omega-Prime" and "MINDO" methods.