First Example of Predominant β-Orientation in Electrophilic Substitution of Pyrrole

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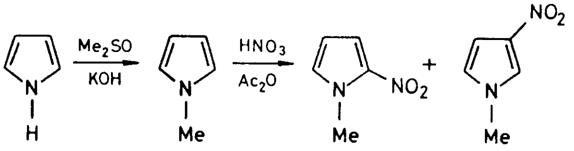
Summary The isomeric distribution of the neutral products from the gas-phase electrophilic attack of $^3He^3H^+$, $CH_3FCH_3^+$, and t-$C_4H_9^+$ ions on pyrrole provides the first experimental evidence for predominant β-orientation in electrophilic substitution of pyrrole [β:α:N = 2·5:2·0:1·0 ($^3He^3H^+$); 1·4:0·4:1·0 ($CH_3FCH_3^+$); 10·3:3·0:1·0 (t-$C_4H_9^+$)].

Electrophilic substitution in the parent five-membered heteroaromatic compounds with one heteroatom occurs predominantly at the α-position.[1] This behaviour has been explained theoretically in terms of the most common semi-empirical reactivity indices, such as frontier electron density, localization energy, *etc.*;[2] on the basis of a transition state involving the heteroaromatic molecule perturbed by the interaction with the electrophile, these methods invariably predict predominant α-substitution for the parent heterocycles and, in the case of pyrrole, reactivity in the order α > β > N.[3] On the other hand, semiempirical and *ab initio* calculations of the π-electron and total charge densities, which would reflect the intrinsic properties of the unperturbed heteroaromatic molecule to orient the electrophile, do not exclude predominance of β-substitution of pyrrole, although the reliability of this approach depends critically on the method of calculation.[4] This view is corroborated by calculation of the ground-state molecular potentials for the interaction between a positive point charge and an isolated pyrrole molecule. The relevant equipotential energy contours show, in fact, that the β-position of the pyrrole ring should be the preferred site of attack for an approaching charged electrophile.[5]

In view of these considerations, and of the profound effect of the environment on several physicochemical properties of pyrrole, related to its electron-density distribution (*e.g.* the overall dipole moment),[4b,6] we have attempted to verify whether the predominant α-orientation for electrophilic substitution observed in solution is a general *intrinsic* feature of the heteroaromatic compounds or is rather determined by environmental factors. To this aim, we have measured the isomeric composition of the products from the electrophilic attack on pyrrole by the ionic species $^3He^3H^+$, $CH_3FCH_3^+$, and t-$C_4H_9^+$, in the gas phase and in the absence of counter-ions.† These ionic species were selected in order to investigate the directive properties of pyrrole with electrophiles of very different reactivity. Thus, the $^3He^3H^+$ ion is a very powerful, relatively unselective Brönsted acid,[7] $CH_3FCH_3^+$ is a pure methylating agent with a rather indiscriminate reactivity with aromatic compounds[8] whereas the t-$C_4H_9^+$ cation is a very mild alkylating species.[9] The decay of molecular tritium in the presence of the gaseous substrate provides a simple and convenient technique for the introduction of $^3He^3H^+$ ions into gaseous systems at any desired pressure, the partial pressure of pyrrole being 10 Torr in the present investigation, and to study their reactions by conventional tracer techniques.[7,10] The method was applied under conditions which excluded interference from radiolytic processes. The distribution of tritium in the labelled pyrrole from the $^3He^3H^+$ ion attack was determined by measuring the decrease of its molar radioactivity caused by the replacement of the tritium atoms by suitable inactive groups, under conditions where no appreciable hydrogen scrambling in the labelled intermediates takes place [reaction (1)].‡



(1)

A useful route to gaseous $CH_3FCH_3^+$ and t-$C_4H_9^+$ ions over a wide pressure range is based on the γ-radiolysis (^{60}Co source, T 37·5 °C) of suitable precursors, namely CH_3F[8] and neopentane,[9,11] respectively. The ions thus generated were allowed to react with trace amounts of pyrrole (*ca.* 1 Torr) in the presence of a powerful radical scavenger (O_2; 4 Torr), which excludes interference from parasitic nonionic pathways, and of an efficient ion trap (NMe_3; 10 Torr). The isomeric products from the reaction of $CH_3FCH_3^+$ and t-$C_4H_9^+$ were identified by g.l.c., by comparison of their retention volumes with those of authentic samples, and their identities confirmed by g.l.c.–mass spectrometry.

Table. Gas-phase electrophilic substitution of pyrrole.[a]

	Composition						Product distribution (%)		
System	Pyrrole, P/(Torr)	Precursor gas (P/Torr or mCi)	NMe_3, P/Torr	O_2, P/Torr	Electrophile	Products	N	α	β
(a)	10	$^3H_2$ (2 mCi)	—	4	$^3He^3H^+$	^3H-Pyrroles	18	37	45
(b)	0·8	CH_3F (745 Torr)[b]	10	4	$CH_3FCH_3^+$	Methylpyrroles	35	15	50
(c)	0·7	neo-C_5H_{12} (745 Torr)[b]	10	4	t-$C_4H_9^+$	t-Butylpyrroles	7	21	72

[a] Standard deviations for product distribution *ca.* ±10%. [b] Radiation dose 4·8 Mrad (dose rate 0·35 Mrad h^{-1}).

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† As is evident from the methods for the preparation of the electrophiles the counter-ion of the ionic electrophile is an electron, which, in the gas-phase, easily escapes from the positively charged electrostatic field of the ion which is formed, and is consequently far removed from the reactant.

‡ The extent of hydrogen scrambling within the labelled pyrrole, and of the tritium loss to the medium, was evaluated by repeating reaction (1) with suitably deuteriated pyrroles.

The Table gives the isomeric composition of the substituted products from the electrophilic attack of the selected ionic reactants on gaseous pyrrole, together with the composition of the systems. Formation of the products in the Table is a major reaction channel in all the systems investigated. The Table shows the predominant formation of β-substituted pyrroles from the radiolytic experiments (b) and (c).

The conditions used in the radiolytic experiments, in particular the high pressure of the gaseous system (760 Torr), which ensures efficient collisional quenching of the ionic intermediates, formed from the exothermic attack of the $CH_3FCH_3^+$ or t-$C_4H_9^+$ ion on pyrrole,[§] and the presence of 10 Torr of NMe$_3$, which minimizes their secondary isomerization by fast neutralization, allow the establishment of a direct correspondence between the isomeric distribution of neutral alkylated pyrroles in the Table and the relative abundances of the charged intermediates formed in the kinetically significant step of the electrophilic alkylation, *i.e.*, the *inherent* directive properties of the substrate toward gas-phase electrophilic substitution.

The same arguments do not necessarily apply to the $^3He^3H^+$ experiments (a). In this case, in fact, the level of excitation of the tritiated adducts is much higher than that of the alkylated adducts of runs (b) and (c),[¶] and the total pressure of the system is much lower (14 Torr). Therefore, occurrence of partial tritium scrambling within the charged adducts cannot be excluded.[**] In spite of this, and of the low selectivity expected for the $^3He^3H^+$ ion, a slight preference of the electrophile for the β-position of pyrrole is still evident, which corroborates the results of the radiolytic experiments.

In conclusion, the reactivity pattern for the gas-phase experiments shows the distinct tendency of pyrrole to direct ionic electrophiles towards the most negatively charged carbon atoms. These findings are in agreement with the most common ion–polar molecule collision theories which indicate that the attractive electrostatic interaction between the ionic electrophile and the negative end of the polar substrate is one of the main factors governing site selection in gas-phase ion–molecule reactions.[12] However, the dependence of the isomeric distribution of the substituted pyrroles upon the nature of the ionic electrophile (see the Table) indicates that other factors, related to the structural and electronic features of the ionic reactant, may be operative.

These results, obtained in the dilute gaseous state, where the intrinsic orienting properties of pyrrole are least affected by those extraneous and variable phenomena (solvation, ion-pairing, catalyst, *etc.*) which invariably complicate electrophilic heteroaromatic substitution in solution, provide direct experimental support for the idea that predominant β-attack on pyrrole may occur,[4,5] the general preference for α-substitution in solution confirming the profound influence of the reaction environment upon its electronic properties and therefore, upon its intrinsic reactivity features.

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[§] Methylation of pyrrole by CH_3FCH^+ ion (ΔH^0 161 ± 8 kcal mol^{-1}: J. L. Beauchamp, D. Holtz, S. D. Woodgate, and S. L. Patts, *J. Am. Chem. Soc.*, 1972, **94**, 2798) is computed to release *ca.* 70 kcal mol^{-1}. Condensation of t-$C_4H_9^+$ (ΔH^0 162 kcal mol^{-1}: R. G. McLoughlin and J. C. Traeger, *J. Am. Chem. Soc.*, 1979, **101**, 5791) is exothermic by *ca.* 35 kcal mol^{-1} (1 cal = 4·184 J).

[¶] The exothermicity of $^3He^3H^+$-ion (ΔH^0 320 kcal mol^{-1}: ref. 7) attack on pyrrole (proton affinity 213 kcal mol^{-1}; D. H. Aue, H. M. Webb, and M. T. Bowers, *J. Am. Chem. Soc.*, 1976, **98**, 318) is exothermic by 168 kcal mol^{-1}.

[**] It must be pointed out, however, that protium rather than tritium scrambling should take place in partially tritiated pyrrole, on account of the large kinetic isotope effect.

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