Reactivity of Indoles in Electrophilic Substitution

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Summary The relative reactivities of a number of indole derivatives in the Vilsmeier–Haack formylation have been determined by a competitive procedure; the data are discussed in terms of possible substitution mechanisms.

RECENTLY special emphasis has been placed on the importance of the electrophilic substitution mechanism in the indole system, especially in connection with biochemical problems. In continuation of our studies on electrophilic substitutions[1] of five-membered heteroaromatic rings, we report here preliminary data for the relative reactivities of a number of indole and pyrrole derivatives in the Vilsmeier–Haack formylation.

A competitive procedure was used. Mixtures of two substrates in *NN*-dimethylformamide were treated at 25° with a solution containing insufficient $POCl_3$ in the same solvent. The mixtures were quenched, worked up as usual ($CHCl_3$ as extracting solvent) and analysed by g.l.c. Relative rates and positions of substitution (from literature data) are summarized in the Table.

Relative reactivity in formylation of pyrrole and indole derivatives

Compound	Overall relative rate	Position of substitution
2-Methylindole	9·2	3
N-Methylpyrrole	2·6	2
Pyrrole	2·2	2
N-Methylindole	2·1	3
Indole	1	3
2,3-Dimethylindole	0·43	1
3-Methylindole	0·40	1 (95%); 2 (5%)
1,2,3-Trimethylindole	0·11	Carbocyclic ring

The main features are as follows.

(a) The reactivity of the β-position of indole is similar to that of the α-position of pyrrole ($k_I/k_P = 0{\cdot}91$ allowing for the statistical factor). These data, which represent the first quantitative comparison of reactivity between these two heterocyclic systems in electrophilic substitution, are in substantial agreement with the relative rates of solvolysis of 1-(1-methylpyrrol-2-yl)- and 1-(1-methylindol-3-yl)-ethyl acetates in aqueous ethanol ($k_I/k_P = 1{\cdot}3$).[2]

(b) *N*-Methylation causes a slight increase in the reactivity of both systems. This indicates that the main reaction path in the substitution of indole and pyrrole does not involve the conjugate base. This increment is smaller in pyrrole, probably owing to a primary steric effect exerted by the methyl group on the reactivity of the α-position.

(c) A plot of the logarithms of the relative rates *vs.* pK_a values of the conjugate acids[3] for indole, 2-methylindole, and *N*-methylindole is linear,[4] since protonation always takes place on C-3. Points for 3-substituted indoles lie below this line, which seems to exclude substitution of 3-methylindole proceeding *via* a preliminary rate-determining attack at the 3-position and subsequent rearrangement to the 3-methyl-2-formyl derivative, as recently suggested for other electrophilic substitutions of 3-alkylindoles.[5]

(d) The relative rates and isomer distributions for 2- and 3-methylindole allow indirect calculation of the β:α reactivity ratio, assuming the same *ortho*-activation by methyl in the two compounds. The value obtained ($\beta/\alpha = 460$) is meaningful only if substitution at α- and β-positions occurs by the same mechanism.

(e) When position 3 is occupied and position 1 is free, substitution occurs mainly at the latter position. At present we have no experimental evidence supporting any particular mechanism. In our opinion the most reliable paths for reactions leading to *N*-substituted products involve the conjugate bases or the indolenine tautomers. Other mechanisms, such as direct attack on nitrogen of the neutral indole form, or attack on position 3, followed by a slow intra- or inter-molecular rearrangement, although they cannot be excluded, seem less likely. Choice between the various hypotheses requires knowledge of the kinetic equation and effects of different substituents on the isomer distributions.

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