# Rates of Reaction of Cyclic Imines with *p*-Fluoronitrobenzene

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Rates of reaction of the cyclic imines from aziridine to octamethyleneimine inclusive, piperazine, and octahydro-1,5-diazocine with *p*-fluoronitrobenzene in dimethyl sulphoxide at 50° have been determined. Azetidine is the most reactive imine.



ARYLATION of azetidine by suitably activated aryl-bromides and aryl methyl ethers is a route to *N*-aryl-azetidines.[1] We have measured the rates of reaction of various cyclic imines with *p*-fluoronitrobenzene to compare the reactivity of azetidine with the other members of the series. Suhr has shown that reaction between amines and *p*-fluoronitrobenzene in dimethyl sulphoxide, which is first order in halide, is also first order in amine to moderately high amine concentrations and that the reaction involves rate-determining C–N bond formation.[2] Thus, the relative rates of *p*-nitrophenylation provide a measure of the nucleophilicities of the cyclic imines.

## EXPERIMENTAL

*Imines.*—Aziridine, b.p. 56° (lit.,[3] 55—56·5°) was prepared from ethanolamine *via* 2-aminoethyl hydrogen sulphate.[3] Azetidine was obtained by reductive cleavage of toluene-*p*-sulphonazetidide,[4] itself prepared from 1,3-dibromopropane and toluene-*p*-sulphonamide. It had b.p. 62·5° (lit.,[5] 62·5°), τ ($CCl_4$) 6·47, (4H, t, *J* 7 Hz), 7·78 (2H, q, *J* 7 Hz) and 8·10 (1H, s). Octahydrodiazocine was collected after the distillation of the azetidine, b.p. 186—190° (lit.,[1] 186—190°). Pyrrolidine and piperidine were commercial products. Hexamethyleneimine, b.p. 138° (lit.,[6] 136—137°) was prepared from cyclohexanone *via* the oxime and 2-oxohexamethyleneimine.[6] Heptamethyleneimine, b.p. 83·5—84·5°/50 mm. (lit.,[6] 57—60/17 mm.) was similarly prepared from cycloheptanone.[6] Octamethyleneimine was a commercial product. Piperazine was isolated from a commercial sample of the adipate. For final purification the imines were distilled from sodium through an 18-in. spinning-band column. Impurities were monitored by gas chromatography and in no case did these amount to 2% in the final product.

*Reagents.*—Dimethyl sulphoxide (Crown Zellerbach) dried over 4A molecular sieve, distilled below 70° under reduced pressure, and was stored over molecular sieve. It had m.p. 18·2° (lit.,[7] 18·45°). Fluka ' purum ' *p*-fluoronitrobenzene was used.

*N-Arylimines.*—The product *N*-(*p*-nitrophenyl) cyclic imines were obtained in quantitative yield by reaction of an excess of imine with *p*-fluoronitrobenzene. Excess of imine was steam distilled from the solution, made alkaline with sodium hydroxide, and the arylimine recrystallised from ethanol. Physical properties, and analytical date for new compounds, are listed in Table 1.

*Kinetics.*—A solution (2 cm.$^3$) of the imine (0·03—0·8 mol. dm.$^{-3}$) in dimethyl sulphoxide was added to a solution of *p*-fluoronitrobenzene in dimethyl sulphoxide (20 cm.$^3$) at 50°c. Samples (2 cm.$^3$) were withdrawn at measured time intervals, quenched in propan-2-ol and made up to 50 cm.$^3$ with the same solvent. The extent of reaction in each sample was evaluated from measurement of the decadic absorbance of the product at the maximum at *ca.* 390 nm. (values of $\varepsilon_{max.}$ are listed in Table 1). Except with aziridine the reactants had negligible absorbance at the analytical wavelength. The absorbance of the solvent dimethyl sulphoxide was low and was balanced by the use of the same dimethyl sulphoxide propan-2-ol solution in the reference. The absorption maximum of *N*-(*p*-nitrophenyl)aziridine occurs at 320 nm. and correction for the overlap with the absorption of *p*-fluoronitrobenzene ($\lambda_{max.}$ 263 nm.) was made by assuming that the total absorption at 263 nm. was due to *p*-fluoronitrobenzene. Use of the relative absorptions of pure *p*-fluoronitrobenzene at 320 and 263 nm. allowed its contribution to the absorption at 320 nm. to be derived. Second-order rate constants were evaluated from the slopes of plots of the integrated form of the second-order rate

TABLE 1

Physical properties and analysis of *N*-(*p*-nitrophenyl) derivatives of cyclic imines

| Imine | M.p./°c (lit., m.p./°c) | $\lambda_{max.}$/nm. | $\varepsilon_{max.}$/m.$^2$ mol.$^{-1}$ | Found (%) C | Found (%) H | Required (%) C | Required (%) H |
|---|---|---|---|---|---|---|---|
| Aziridine | 84·5(82) | 320·5 | 1180 | | | | |
| Azetidine | 118—120 (119) | 384 | 1960 | | | | |
| Pyrrolidine | 169·5 (167) | 391·5 | 2200 | | | | |
| Piperidine | 105 (105) | 389 | 1900 | | | | |
| Hexamethyleneimine | 76 (77) | 395 | 2260 | | | | |
| Heptamethyleneimine | 89 | 390 | 2270 | 66·6 | 8·0 | 66·7 | 7·7 |
| Octamethyleneimine | 146 | 393 | 2230 | 67·6 | 8·0 | 67·7 | 8·1 |
| Piperazine | 131 | 383 | 1780 | 58·3 | 6·6 | 58·0 | 6·3 |
| Octahydro-1,5-diazocine | 134 | 393 | 2160 | 60·8 | 7·5 | 61·3 | 7·2 |

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equation. For each amine two to four independent values of the rate constant were determined. The standard deviation of the rate constant for each amine was less than 5% of the mean rate constant except with octamethyleneimine (10%). Again, with the exception of octamethyleneimine when the value was 20% high, the measured concentration of the product *N*-(*p*-nitrophenyl)imine after 50 half-lives was within 4% of the value calculated for complete reaction. Variation of the initial concentration of imine did not affect the rate constant. Rate constants are listed in Table 2.

TABLE 2

Rate constants for reaction at 50° of cyclic imines with *p*-fluoronitrobenzene in dimethyl sulphoxide

| Imine | $k$/dm.$^3$ mol.$^{-1}$ ksec.$^{-1}$ | Lit. values [8] |
|---|---|---|
| Aziridine | 0·42 | 0·51 |
| Azetidine | 126 | 38 |
| Pyrrolidine | 69·6 | 52 |
| Piperidine | 33·9 | 28 |
| Hexamethyleneimine | 18·0 | 13·8 |
| Heptamethyleneimine | 0·54 | |
| Octamethyleneimine | 0·59 | |
| Piperazine | 55·4 | |
| Octahydrodiazocine | 41·8 | |

Some rate constants, necessarily less accurate, were determined for reactions in which excess of *p*-fluoronitrobenzene was used. These were in satisfactory agreement with those listed in Table 2. In dimethyl sulphoxide solution the hydrogen fluoride released in the reaction did not appear to inhibit the complete arylation of the imine since piperidine was quantitatively converted to *N*-(*p*-nitrophenyl)piperidine by excess of *p*-fluoronitrobenzene. Even piperidine hydrofluoride was quantitatively arylated with *p*-fluoronitrobenzene and the rate of arylation of the hydrofluoride differed from that of piperidine itself by less than 10%. Thus the extent of protonation of the imines by hydrogen fluoride in dimethyl sulphoxide must be small.

## DISCUSSION

After the inception of the present work Suhr reported the rates of reaction of the imines from azetidine to hexamethyleneimine inclusive with *p*-fluoronitrobenzene.[8] His values are also shown in Table 2 and it may be noted that there is a substantial disagreement between his and our rate constants for azetidine. We repeated our preparation of azetidine and the second sample gave the same rate constant as the first. Both samples gave only one peak on gas chromatographic analysis with a variety of columns. The n.m.r. spectrum confirmed the azetidine structure and the quintet and triplet patterns were closely similar to those of an authentic sample of *N*-phenylazetidine. Suhr prepared his azetidine by the same method that we used, but he does not report the careful fractional distillation essential for the removal of close-boiling impurities and octahydro-1,5-diazocine.[1] The b.p. reported by Suhr was 67°, significantly higher than the literature value of 62·5°, reconfirmed in our study. Suhr obtained only a low yield (40%) of *N*-(*p*-nitrophenyl)azetidine from his azetidine.

Our results show that azetidine is the most nucleophilic imine. There is a uniform decrease in reactivity from azetidine through to hexamethyleneimine and a marked decrease with heptamethyleneimine and octamethylenimine which are almost as unreactive as aziridine. A similar dependence on ring size has been observed for other reactions of these cyclic imines *viz.* equilibrium protonation [5,9] and equilibrium complex formation with trimethylboron.[10] In both reactions aziridine is the least-reactive imine and azetidine the most reactive. Brown has discussed the factors which control the reactivity of cyclic compounds and, in particular, the cyclic imines.[10,11] The low reactivity of aziridine is explicable in terms of the overwhelming importance of bond-angle distortion in the three-membered ring; angle strain is claimed to be greater in the conjugate acid with a four-co-ordinated nitrogen atom than in the free imine and, similarly, angle strain should be greater in the transition state for arylation than in the free imine.* Although the reactivity of azetidine relative to the larger-ring imines should also be reduced by angle strain the effect of this is much less than in aziridine. Moreover, there is less steric interaction between the imine and aryl components in the transition state (*F*-strain) with the four-membered ring than with the higher-ring imines. The latter factor appears to be more important than angle strain in azetidine so that the common (5—7) ring imines are less reactive than azetidine. The very low reactivity of heptamethyleneimine and octamethylenimine may be attributed to a transannular steric interactions, such interactions plausibly being greater in the transition state for arylation than in the free imine.

Piperazine is roughly as reactive, per nitrogen atom, as piperidine and octahydrodiazocine is 40 times more reactive per nitrogen atom than heptamethylenimine. The electronic effect of the second nitrogen atom should reduce the nucleophilicity of the first. Clearly, the second nitrogen atom in octahydrodiazocine has a very marked additional accelerating effect. The 1 and 5 positions in eight-membered ring compounds are close because of the 'crown' conformation of the large ring.[13] Interactions and hydride shifts between these

* An alternative explanation of the low nucleophilicity of aziridine is based on hybridization arguments. In the three-membered ring, the orbitals used to form the ring bonds have high *p*-character and hence the external bonds involve orbitals of high *s*-character.[12] In the transition state for quaternization, the developing N–C bond will likewise involve an orbital on nitrogen of higher than normal *s*-character. Use of such an orbital results in poorer overlap, a less-stable partial bond and a higher energy transition state.

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positions are known to occur.[14] Octahydro-1,5-diazocine can therefore adopt a conformation in which the nitrogen atoms are close and it is likely that this can lead to transition-state stabilization *e.g.* by hydrogen bonding of the hydrogen atom of the imino-group undergoing arylation to the nitrogen of the second imino-group. Such interaction would transfer some of the positive charge was developing on the first imino-group to the second.

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