Kinetics of the Replacement of the Nitro group from 2- and 4-Nitropyridine by Methoxide Ion in Methanol

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Detailed studies of nucleophilic substitutions in heteroaromatic systems (1) have been mainly focussed on the displacement of halogens, whereas the reactivity of other leaving groups towards nucleophiles has received less attention. Semiquantitative data on the replacement of the nitro and of the sulphonic group by neutral and anionic nucleophiles were reported by Mangini and coworkers in their early studies on nitrogen heterocycles (2a-c), and subsequent synthetic approaches (3) were carried out by other authors. Recently, Barlin and Brown have reported (4) kinetic data on the replacement of the methylsulphonyl group by methoxide ion from several nitrogen heterocycles, and Johnson has investigated (5) the ethoxy and piperidino dehalogenation and denitration of substituted pyridine *N*-oxides.

Nucleophilic aromatic substitutions are affected by a number of factors and in several cases no general rules can be generally applied in order to predict or explain the observed reactivity. For instance, the approximate mobility order (6) of replaceable groups given by Bunnett and Zahler does not seem to be a general rule, as it is not followed in the case of the replacement of the methylsulphonyl group (4) and of halogens (7) by methoxide ion in pyridine derivatives. Furthermore, the matter of the relative reactivities of the *ortho*- and *para*-isomers with regard to the activating group and to the nucleophilic reagent should be enlarged to include the type of leaving group. In this sense the quantitative data on nucleophilic displacements of different leaving groups in heteroaromatic systems can be helpful in establishing an order of mobility

TABLE I

Kinetics of the Reaction of Sodium Methoxide in Methanol with Nitropyridines

4-Nitropyridine, 0.0181 *M*; Methoxide ion, 0.0435 *M* (35°).

Time (min.)	19	44	67	114	144	174	204	266	1080
Reaction (%)	6	15	20	30	37	43	48	56	93
10^3k (l. mole^{-1} sec.$^{-1}$)	1.21	1.42	1.38	1.34	1.38	1.40	1.42	1.41	1.45

Mean 10^3k = 1.38±0.04; corrected for solvent expansion, 1.39

2-Nitropyridine, 0.00354 *M*; Methoxide ion, 0.0765 *M* (50°).

Time (min.)	165	306	429	588	1248	1367	1471	1601	1763
Reaction (%)	12	21	29	39	64	65	69	70	74
10^4k(l. mole^{-1} sec.$^{-1}$)	1.64	1.72	1.74	1.70	1.78	1.67	1.71	1.64	1.66

Mean 10^4k = 1.69±0.04; corrected for solvent expansion, 1.74

TABLE II

Rate Constants and Arrhenius Parameters for the Reaction of Methoxide Ion with Nitropyridines in Methanol.

Nitropyridine	$10^4 k_2$ (a) (l. mole^{-1} sec.$^{-1}$)				E_a (b) (kcal. mole^{-1})	log A (c)	$\Delta S\neq$ (d) (e.u.)
	25°	35°	50°	70°			
2-Nitro		0.35	1.66	13.9	22.0	11.1	-9.8
4-Nitro	4.50	13.9	63.0	340	19.5	11.0	-10.3

(a) Mean values of three or more independent runs. Standard deviation was about 2%. (b) Accurate to ± 0.3 kcal. mole^{-1}. (c) At 50°, accurate to ± 0.3 unit. (d) At 50°, accurate to ± 1.5 e.u.

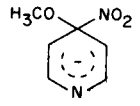
in connection with the type and the position of the activating group and with the characteristics of the nucleophile.

Rate data and some thermodynamic parameters for the reaction of 2- and 4-nitropyridine with sodium methoxide in anhydrous methanol are herein reported. Under the kinetic conditions used, the nitropyridines gave the corresponding ethers which have been recovered in high yield (70-80%) and identified by their physical and spectroscopic properties.

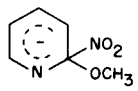
The reactions of 2- and 4-nitropyridine which were followed by ultraviolet spectroscopic analysis at 238 and 285 mμ, respectively, were shown to be second-order processes and first-order with respect to the nitropyridine and to the methoxide ion when the initial concentration of both reagents was varied by a factor of 10. Typical runs are reported in Table I, whereas Table II summarizes the kinetic results and the derived activation parameters.

From these reported kinetic data it appears that the displacement of the nitro group by methoxide ion in methanol follows the second-order kinetic law, which is consistent with a bimolecular mechanism. However, at present the direct experimental evidence does not indicate whether the reaction proceeds by a one-step or a two-step path, although the latter is the most accepted for similar systems (4,5).

From the rate constants listed in Table II it appears that 4-nitropyridine is more reactive than the 2-isomer towards methoxide ion in methanol, the *para:ortho* ratio being greater than unity over the whole range of temperatures investigated (k_p/k_o = 38 at 50°). Similar results have been reported for the displacement of the chloro (7,8) and of the methylsulphonyl group (4) by alkoxide ion in aromatic heterocyclic bases and for the displacement of chloro (9) from chloronitrobenzenes. The greater reactivity of 4-nitropyridine is mainly related to the lower activation energy (19.5 kcal./mole) compared to that of the 2-isomer (22.0 kcal./mole), since the variation of the entropy factor is within the limits of experimental error. If a two-stage mechanism is followed, the differences in rate could be ascribed to specific solvation effects on the stability of the intermediate complexes (Ia) and (Ib), as it has been recently reported for similar systems (10).



(Ia)



(Ib)

However, the greater reactivity towards alkoxide ions of the 4-isomer with respect to that of the 2-isomer is not a general finding, this being dependent on the activating group and the type of alkoxide ion. *Para:ortho* ratios lower than unity have been reported for the displacement by ethoxide ion of the nitro group and of bromo from pyridine *N*-oxides (5) and for the reaction of sodium methoxide with chloro-*N*-methylpyridinium compounds (7). Moreover, *para:ortho* ratio has been found to be reversed by increasing the size of the alkoxide ion in aromatic substitutions of halogens activated by the nitro group (11).

In pyridine derivatives the nitro group in both positions 2- and 4- is a much better leaving group towards sodium methoxide than either the methylsulphonyl or chloro groups. This is substantiated by a direct comparison of

our results with those reported by Liveris and Miller (7) and with the extrapolated rate constants (12) obtained from the data of Barlin and Brown (4). The relative rates of displacement of nitro, methylsulfonyl and chloro from the 4-derivatives by sodium methoxide are 7080:154:1 and those from the 2-derivatives are 5060:65:1 at 50°. This greater reactivity of the nitro group compared to that of methylsulphonyl and chloro results from a lower activation energy which compensates for the decrease of the entropy factor. Even if expected (5,6,13) these ratios of reactivity seem to be the largest reported to date.

EXPERIMENTAL

Materials and Products.

Methanol was purified by the magnesium method (14). Nitropyridines were prepared by known methods and purified by sublimation *in vacuo* (0.5 mm.): 2-Nitropyridine (2a, 15), m.p. 70-71°; 4-nitropyridine (16), m.p. 50-51°. The 2- and 4-methoxypyridines were obtained from the corresponding nitro derivatives and sodium methoxide in absolute methanol according to the procedure previously described by one of us (2a). The products were recovered from the reaction mixture by dilution with water and extraction of the water-methanolic mixture with ethyl ether. After evaporation of the ether, the oily residue was distilled: 2-methoxypyridine, b.p. 141-142° (Lit. (17) 144°), λ max (methanol) 270 mμ (log e 3.62) (17), picrate m.p. 163-164° (from ethanol) (2a, 4); 4-methoxypyridine, b.p. 95°/30 mm. (Lit. (18) 95-96°/31 mm.), λ max (methanol) 219 mμ (log ε 3.76) (19), picrate m.p. 172-173° (from ethanol) (4).

Kinetics.

Kinetic runs were followed by measuring the decrease in absorbance near one of the absorption maxima of the nitropyridines after appropriate dilution of samples (10- to 5-fold) with water. The condentrations of nitropyridines in the quenched solutions were between 10^{-4} and 10^{-5} *M* and Beer's law was obeyed. The analytical wavelengths were: 238 mμ (log ε 3.66 in methanol/water, 1:10) for 2-nitropyridine and 285 mμ (log ε 3.24 in methanol/water, 1:10) for 4-nitropyridine. Small variations of ε were observed by changing the dilution. At the indicated wavelengths 2- and 4-methoxypyridine showed a negligible absorption.

In the case of reactions carried out at 25° or 35°, the solusions of 2- or 4-nitropyridine and sodium methoxide (this was standardized with sulphuric acid, 0.1 or 0.01 *N*) in methanol were prepared and thermostatted in volumetric flasks. Aliquots of the solutions of the two reagents were mixed in a round-bottomed flask and samples of 2 or 5 ml. were removed at intervals. The samples were diluted with water and the absorption of the quenched solutions was determined at the appropriate wavelength by means of a Beckman Model DU spectrophotometer.

In the case of experiments carried out at 50° and 70°, the reaction solution was prepared at 25° by combination of appropriate volumes of standard methanolic solutions of reactants. Portions of this reaction mixture (2- or 5-ml.) were then sealed in Pyrex ampoules and placed in the thermostat at the same time. The ampoules were removed at intervals, plunged into cold water, and opened; the contents were then transferred quantitatively to volumetric flasks and, after dilution with water (50 or 100 ml.), the absorption at the appropriate wavelength (see above) was measured.

Rate coefficients were calculated by graphical or analytical treatment of the experimental data according to the pseudo first-order kinetic equation when a large excess of methoxide ion was used, or according to the second-order kinetic equation in the other cases. Appropriate corrections of the rate coefficients were made for the expansion of the solvent.

Experimental values for k_2 (see Table II) determined at the same temperature did not differ by more than 2-3% in independent runs. The initial concentrations of the reagents were 0.002-0.01 *M* for the nitropyridines and 0.03-0.1 *M* for methoxide ion. The energy of activation, E_a, and the frequency factor, $\log_{10}A$, were graphically determined by plotting log k vs. 1/T and the entropy of activation, $\Delta S^{\neq}$, was computed from these.

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