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Nucleophilic Reactivity

Part 17.[1] Kinetics of the Reactions of 2-Fluoro-3-nitropyridine and 2-Fluoro-5-nitropyridine With Hydroxide and Alkoxide Ions

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The kinetics of the alkaline hydrolyses and alcoholyses of 2-fluoro-3-nitropyridine and 2-fluoro-5-nitropyridine have been studied at 3 – 5 temperatures in water, methanol and ethanol and in aqueous methanol and ethanol of low alcohol content. The compositions of the reaction products in aqueous alcohols were evaluated and apparent rate constants and activation parameters computed. It was found that both a nitro group and an aza nitrogen in a position *ortho* to the fluorine atom increase the rate of reaction with hydroxide ion and decrease the rates of reactions with alkoxide ions relative to the *para* compounds. The alkoxide/hydroxide reactivity ratio is nearly the same whether a nitro or an aza group is in position *ortho* to the fluorine atom.

In previous parts of this series, the reactions of 2,4-dinitrofluorobenzene (2,4-DNFB),[2,3] 2,6-dinitrofluorobenzene (2,6-DNFB),[1] picryl fluoride,[4] and dinitrobenzenes [5,6] with hydroxide and alkoxide ions in aqueous alcohols were discussed. As an aza nitrogen accelerates nucleophilic substitution reactions to about the same extent as a nitro group,[7] 2-fluoro-3-nitropyridine (3-NFP) and 2-fluoro-5-nitropyridine (5-NFP) should react at rates comparable to those of nitrobenzenes. As steric effects due to *ortho* nitro groups are less marked in the pyridine compounds than in their benzene analogues or are absent, the reactions of the former were studied, mainly to obtain information about the influence of *ortho* nitro groups on the rates of hydroxylation and alkoxylation and on the reactivity ratios. The alkaline hydrolyses of fluoronitropyridines seem not to have been studied previously.

EXPERIMENTAL

3-NFP, m.p. 17.8 ± 0.2°, and 5-NFP, m.p. 17.3°, b.p. 91.0 – 91.5°/10 mmHg, were synthesized according to Finger and Starr.[8] Methanol (Guaranteed Reagent from E. Merck) and ethanol (Spectrograde, from the Finnish State Alcohol Monopoly) were treated with magnesium methoxide according to Lund and Bjerrum.[9] The water was triply distilled (in the first distillation, some $KMnO_4$ was added, in the second, $Ba(OH)_2$). The solutions of alkali were made from "Titrisol" sodium hydroxide (from E. Merck), or by dissolving sodium in alcohol.

The kinetic method was essentially the same as previously.[2] The nitro compound was dissolved in the alcoholic component of the solvent (for the reactions in water, in a small amount of dioxane; its content in the final reaction mixture was about 0.1 %). The reactions were carried out in two-compartment reaction vessels.[10] As the pK_a's of the hydroxy compounds are about 7, a neutral buffer could not be used to stop the reactions. The reactions were retarded by adding boric acid buffer of pH 10, except in the case of 5-NFP in alcohol-water mixtures, where no buffer was used. The absorbances of the formed hydroxylation products were measured as rapidly as possibly with a Unicam SP 600 spectrophotometer; the reaction did not proceed significantly during this stage because of low initial concentrations of alkali (0.005 M in mixed solvents) and added buffer. The wavelength was 390 nm in the case of 3-NFP and 365 nm in the case of 5-NFP. Cells of 4 cm path length were used because of the low solubilities of the nitro compounds (the initial concentrations of the nitro compounds in water and aqueous alcohols were $2-5\times10^{-5}$ M).

The final concentration of the hydroxylation product was determined by letting the reaction mixture stand in a thermostat for ten half-lives (the reaction was run under pseudo first order conditions). Small corrections were applied for the hydrolysis of the nitropyridyl ethers; the kinetics of these reactions were studied previously.[11] By heating the reaction mixture in a sealed ampoule for several hours at 100°, also the nitropyridyl ether hydrolysed completely and the initial concentrations of the fluoronitropyridine could thus be determined.

The initial concentrations of both components in the anhydrous alcohols were 0.02 M. The reaction was arrested with hydrochloric acid, and the excess acid was titrated with barium hydroxide.

The rate constants and activation parameters were computed as previously.[2,6, *cf.* also 12] The rate constants were corrected for the thermal expansion of the solvent.

The non-SI units used were: 1 cal = 4.184 J, and 1 M = 1 mol dm^{-3}.

RESULTS AND DISCUSSION

The results of the measurements are collected in Tables 1 – 4. In these, x is the concentration of the formed pyridyl ether, y that of the formed hydroxyl compound (x/y is thus the product ratio), the subscript h refers to hydroxide, m to methoxide, e to ethoxide and a to alkoxide ion. The rate constants and activation parameters for the reactions are apparent quantities because of the influence of the hydroxide-alkoxide equilibrium.[2,6,12] The product composition quantities B_{ha}' were computed from the expression [2,6,12]

$$B_{ha}' = \frac{x\, x_{H_2O}}{y\, x_{AlkOH}} = \frac{k_a^\circ}{k_h^\circ} K_{ha}' \qquad (1)$$

where k_a° and k_h° are the rate constants of the reactions with alkoxide and hydroxide ions corrected for the hydroxide-alkoxide equilibrium, and K_{ha}' is the hydroxide-alkoxide equilibrium constant.[2,6,12]

Table 5 was constructed to enable a comparison with the corresponding benzene compounds (reactivity ratios for several other compounds are given in Ref. 12).

The following conclusions can be drawn on inspection of the tables:

(i) The reactions of the halogenonitropyridines are slower than the corresponding reactions of the halogenonitrobenzene analogues (see also Refs. 1, 7, 13, and 14). Thus 2,4-DNFB reacts with hydroxide and alkoxide ions

Table 1. Rate constants ($M^{-1}\ s^{-1}$), activation energies (kcal mol^{-1}) and logarithms of frequency factors for the reactions of 2-fluoro-3-nitropyridine with hydroxide ion (subscript h) and with methoxide ion (subscript m) in methanol-water mixtures. The initial concentration of alkali (sodium hydroxide + methoxide) was 0.01 M in water, 0.005 M in the methanol-water mixtures and 0.02 M in methanol.

Wt. % MeOH	x_{MeOH}	$t°$	x/y	k_h	k_m	E_h	E_m	log A_h	log A_m	$E_h - E_m$	B_{hm}'
0	0	0.00		0.00288		16.95		11.00			
		15.00		0.0143							
		25.00		0.0382							
		40.00		0.150							
0.857	0.00484	0.00	1.17	0.00292	0.00343	16.85	11.99	10.94	6.20	4.86	241
		15.00	0.726	0.0145	0.0105						149
		25.00	0.560	0.0396	0.0222						115
		40.00	0.371	0.154	0.0570						76
1.65	0.00934	0.00	2.06	0.00314	0.00647	16.75	11.70	10.87	7.17	5.05	218
		15.00	1.27	0.0153	0.0194						134
		25.00	0.943	0.0416	0.0392						100
		40.00	0.628	0.162	0.102						67
3.26	0.0186	0.00	3.98	0.00325	0.0129	16.83	11.99	10.97	7.72	4.84	210
		15.00	2.55	0.0162	0.0412						135
		25.00	1.89	0.0437	0.0828						100
		40.00	1.27	0.172	0.217						67
100.0	1.000	0.00			0.0733		14.39		10.38		
		15.00			0.296						
		25.00			0.680						
		40.00			2.17						

Table 2. Rate constants ($M^{-1}\ s^{-1}$), activation energies (kcal mol^{-1}) and logarithms of frequency factors for the reactions of 2-fluoro-3-nitropyridine with hydroxide ion (subscript h) and with ethoxide ion (subscript e) in ethanol-water mixtures. The initial concentration of alkali (sodium hydroxide + ethoxide) was 0.01 M in water, 0.005 M in the ethanol-water mixtures and 0.02 M in ethanol.

Wt. % EtOH	x_{EtOH}	$t°$	x/y	k_h	k_e	E_h	E_e	log A_h	log A_e	$E_h - E_e$	B_{he}'
5.63	0.0228	0.00	0.764	0.00329	0.00251	16.55	12.70	10.76	7.57	3.85	32.8
		15.00	0.534	0.0164	0.00878						22.9
		25.00	0.420	0.0437	0.0184						18.0
		40.00	0.305	0.162	0.0495						13.1
12.09	0.0517	0.00	1.78	0.00387	0.00688	16.49	12.41	10.78	7.76	4.08	32.6
		15.00	1.21	0.0186	0.0226						22.3
		25.00	0.947	0.0487	0.0461						17.4
		40.00	0.684	0.188	0.129						12.5
14.46	0.0620	0.00	2.57	0.00412	0.0106	16.63	12.19	10.92	7.78	4.44	38.9
		15.00	1.67	0.0201	0.0335						25.2
		25.00	1.28	0.0549	0.0705						19.4
		40.00	0.903	0.203	0.183						13.6
100.0	1.000	0.00			0.104		15.28		11.24		
		10.00			0.285						
		20.00			0.696						
		25.00			1.10						
		40.00			3.84						

Table 3. Rate constants (M^{-1} s^{-1}), activation energies (kcal mol^{-1}) and logarithms of frequency factors for the reactions of 2-fluoro-5-nitropyridine with hydroxide and methoxide ions in methanol-water mixtures. The initial alkali concentrations as those stated in Table 1.

Wt. % MeOH	x_{MeOH}	$t°$	x/y	k_h	k_m	E_h	E_m	log A_h	log A_m	$E_h - E_m$	B_{hm}'
0	0	0.00		0.00143		17.68		11.28			
		15.00		0.00764							
		25.00		0.0214							
		40.00		0.0879							
		50.00		0.209							
1.47	0.00829	0.00	3.71	0.00145	0.00538	17.68	12.94	11.30	8.16	4.74	444
		15.00	2.45	0.00761	0.0187						293
		25.00	1.87	0.0228	0.0426						224
		40.00	1.24	0.0917	0.114						148
2.13	0.0121	25.00	2.74	0.0236	0.0647	17.39	12.91	11.12	8.27	4.48	224
		40.00	1.88	0.0974	0.183						153
		50.00	1.51	0.231	0.349						123
2.22	0.0126	0.00	5.66	0.00170	0.00960	17.21	12.57	10.97	8.02	4.64	443
		15.00	3.76	0.00733	0.0275						294
		25.00	2.84	0.0226	0.0643						222
		40.00	1.91	0.0929	0.178						149
		50.00	1.53	0.217	0.332						120
100.0	1.000	0.00			0.209		14.48		10.90		
		15.00			0.798						
		25.00			1.98						
		40.00			6.15						
		50.00			12.9						

Table 4. Rate constants (M^{-1} s^{-1}), activation energies (kcal mol^{-1}) and logarithms of frequency factors for the reactions of 2-fluoro-5-nitropyridine with hydroxide and ethoxide ions in ethanol-water mixtures. The initial alkali concentrations as those stated in Table 1.

Wt. % EtOH	x_{EtOH}	$t°$	x/y	k_h	k_e	E_h	E_e	log A_h	log A_e	$E_h - E_e$	B_{hm}'
3.37	0.0135	0.00	1.06	0.00178	0.00188	17.17	13.13	10.98	7.77	4.04	77.4
		15.00	0.727	0.00885	0.00644						53.2
		25.00	0.579	0.0245	0.0142						42.4
		40.00	0.403	0.0989	0.0398						29.5
		50.00	0.338	0.237	0.0801						24.8
6.52	0.0265	0.00	2.16	0.00173	0.00373	17.40	13.05	11.15	8.01	4.35	79.2
		15.00	1.48	0.00845	0.0125						54.3
		25.00	1.21	0.0245	0.0296						44.3
		40.00	0.792	0.103	0.0818						29.0
		50.00	0.628	0.238	0.149						23.0
100.0	1.000	0.00			0.627		13.88		10.91		
		8.00			1.30						
		15.00			2.51						
		25.00			5.52						
		40.00			16.3						

Table 5. Comparison of the reactivities of some benzene and pyridine derivatives at 25°. Rate constants are in M^{-1} s^{-1}, energies of activation in kcal mol^{-1}. Abbreviations. 2,4-DNFB: 2,4-dinitrofluorobenzene, 2,6-DNFB: 2,6-dinitrofluorobenzene. 5-NFP: 2-fluoro-5-nitropyridine. 3-NFP: 2-fluoro-3-nitropyridine. PF: picryl fluoride. 1,2-DNB: 1,2-dinitrobenzene. 1,4-DNB: 1,4-dinitrobenzene.

	2,4-DNFB	2,6-DNFB	5-NFP	3-NFP	PF	1,2-DNB	1,4-DNB
$k_h°(H_2O)$	0.129	0.275	0.0214	0.0382	700	0.260×10^{-5}	0.0968×10^{-5}
$k_m°(MeOH)$	15.4	5.53	1.98	0.680	$\sim 10^4$	14×10^{-5}	37×10^{-5}
$k_m°(H_2O)$ [a]	5.5	5.3	1.1	0.85	$\sim 10^4$		
$k_e°(EtOH)$	63	9.38	5.52	1.10	$\sim 10^4$	22×10^{-5}	177×10^{-5}
$k_e°(H_2O)$ [a]	8.1	5.5	1.4	1.1	$\sim 10^4$		
$k_m°/k_h°$	46	19	49	22	15	38	185
$k_e°/k_h°$	63	20	65	28	18	40	200
$E_h°(H_2O)$	16.94	15.39	17.68	16.95	11	23.01	25.56
$E_m°(MeOH)$	13.52	13.70	14.48	14.39		22.0	22.6
$E_e°(EtOH)$	12.66	13.77	13.88	15.28		20.8	22.3
$\log A_h°(H_2O)$	11.53	10.74	11.28	11.00	11	11.28	12.72
$\log A_m°(MeOH)$	11.10	10.80	10.90	10.38		10.8	13.1
$\log A_e°(EtOH)$	11.07	11.07	10.91	11.24		11.6	13.6
Ref.	2	1			4, 12	5, 6, 12	5, 6, 12

[a] Estimated using the value of the hydroxide-alkoxide equilibrium constant mentioned in the text.

5 – 8 times faster than 5-NFP, and 2,6-DNFB reacts 5 – 8 times faster than 3-NFP.

(ii) In water 3-NFP reacts about 2 times faster with hydroxide ion than does 5-NFP. Also in the case of the corresponding benzene compounds the *ortho* nitro-substituted compound reacts faster than the *para* nitro-substituted compound with hydroxide ion. In the case of both the benzene and pyridine compounds, the increase in rate is due to a lower energy of activation; this influence is in part compensated for by a smaller frequency factor, which is obviously due to steric influences.

(iii) 5-NFP reacts about 3 times faster than 3-NFP in methanol and 4 – 6 times faster in ethanol. The slowness of the reactions of 3-NFP is due to lower values of the frequency factor for the reactions with methoxide ion and to greater energies of activation for the reactions with ethoxide ion. Again the differences are similar to those found for the benzene compounds (see also Ref. 15).

If chlorine is the leaving substituent, the differences are still much more marked. Thus 2-chloro-5-nitropyridine reacts 49 times faster than 2-chloro-3-nitropyridine in methanol at 31° with methoxide ion,[14] and 1-chloro-2,4-dinitrobenzene reacts 39 times faster than 1-chloro-2,6-dinitrobenzene with methoxide ion at 50°.[16]

(iv) If we take $K_{hm}' = 4.5$ in methanol-water and $K_{he}' = 0.65$ in ethanol-water mixtures at 25°,[6,12] we obtain the values given in Table 5 for the reactivity ratios, $k_m°/k_h°$ and $k_e°/k_h°$. It is seen that the ratios for 3-NFP are closer to those for substituted benzenes with two nitro groups in positions *ortho* to the site of reaction (2,6-DNFB and picryl fluoride) than to those with only one *ortho* nitro group, and the ratios for 5-NFP are about the same as the ratios for 2,4-DNFB, where there is one *ortho* nitro group. Thus the variation of the replacement ratios with nitro activation seems not to be caused by steric influences alone. However, the ratios for 2,6-DNFB [1] are similar to those for picryl fluoride,[4,12] although the latter compound reacts about 10^3 times faster than the former.

(v) Rate constants for alkoxide reactions often increase when going from water to alcohol. In the case of fluoronitropyridines, this occurs with 5-NFP, but there are no substantial rate changes in the case of 3-NFP. Similarly the increase is much more marked for 2,4-DNFB than for 2,6-DNFB with two *ortho* nitro groups.

(vi) The values of $E_h - E_m$ in methanol-water mixtures and the values of $E_h - E_e$ in ethanol-water mixtures for 3-NFP and 5-NFP are similar to the corresponding values for 2,4-DNFB but are larger than those for 2,6-DNFB.[1]

It has been stated [17] that, all other things being equal, the nitro group is preferentially *ortho* activating. This is seen to hold also in the case of the reactions studied in the present work, if the leaving and coming groups are small like fluorine and hydroxyl. However, if the leaving group (see Ref. 11) or coming group is an alkoxyl, the *para* nitro isomer reacts faster than the *ortho* nitro isomer in the case of both benzene and pyridine compounds. It has often been maintained that steric interference of adjacent substituents will prevent complete attainment of coplanarity of an *ortho* nitro group and thus diminish the activation by the nitro group and hence the reactivity of the *ortho* nitro compound to a level below that of the *para* nitro compound, where the nitro group is unhindered. Such an explanation, although it would explain the low *ortho/para* ratios, seems not very probable in the case of defluoroalkoxylation reactions (bearing in mind also the similar *ortho/para* ratios in alkoxylation and dealkoxylation reactions), and it does not explain the similar k_a°/k_h° ratios for 2,6-DNFB and 3-NFP. This explanation has been criticized also in connection with amination reactions.[18]

Greater activation by *ortho* nitro as compared with *para* nitro in some amination reactions has been explained as being due to internal, "built-in" solvation (*cf.*, *e.g.*, Ref. 16). Such effects could possibly explain the large *ortho/para* replacement ratios in defluorohydroxylation reactions, but not in dealkoxyhydroxylation reactions.

REFERENCES

1. Murto, J., Wartiovaara, I. and Janhonen, J. *Suomen Kemistilehti.* **B 44** (1971) 312. (Part 16.)
2. Murto, J. *Acta Chem. Scand.* **18** (1964) 1029.
3. Murto, J. *Acta Chem. Scand.* **18** (1964) 1043.
4. Murto, J. *Acta Chem. Scand.* **20** (1966) 303.
5. Tommila, E. and Murto, J. *Acta Chem. Scand.* **16** (1962) 53.
6. Murto, J. *Ann. Acad. Sci. Fennicae Ser. A II* **1962** No. 117.
7. Illuminati, G. *Advan. Heterocycl. Chem.* **3** (1964) 285, p. 319.
8. Finger, G. C. and Starr, L. D. *J. Am. Chem. Soc.* **81** (1959) 2674; see also Gruber, W. *Can. J. Chem.* **31** (1953) 1020.

9. Lund, H. and Bjerrum, J. *Ber.* **64** (1931) 210.
10. Tommila, E. and Lindholm, M. *Acta Chem. Scand.* **5** (1951) 647.
11. Murto, J., Nummela, L., Hyvönen, M.-L. and Wartiovaara, I. *Suomen Kemistilehti* **B 43** (1970) 517.
12. Murto, J. In Patai, S., Ed., *The Chemistry of Hydroxyl Group*, Interscience, London and New York 1971, p. 1087.
13. Mangini, A. and Frenguelli, B. *Gazz. Chim. Ital.* **69** (1939) 86.
14. Abramovitch, R. A., Helmer, F. and Liveris, M. *J. Chem. Soc.* **B 1968** 492.
15. Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam 1968, p. 101.
16. Biffin, M. E. C., Miller, J. and Roper, R. *Australian J. Chem.* **22** (1969) 2555.
17. Bunnett, J. F. *Quart. Rev. Chem. Soc.* **1958** 1.
18. Pietra, F. *Quart. Rev. Chem. Soc.* **23** (1969) 504, p. 510.

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