Nucleophilic Reactivity

Part 17. 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 azo 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 azo group is in position ortho to the fluorine atom.

In previous parts of this series, the reactions of 2,4-dinitrofluorobenzene (2,4-DNFB), 2,6-dinitrofluorobenzene (2,6-DNFB), picryl fluoride, and dinitrobenzenes with hydroxide and alkoxide ions in aqueous alcohols were discussed. As an azo nitrogen accelerates nucleophilic substitution reactions to about the same extent as a nitro group, 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. 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.\textsuperscript{4} The water was
tritely distilled (in the first distillation, some KMnO\textsubscript{4} was added, in the second, Ba(OH)\textsubscript{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.\textsuperscript{3} The nitro compound was
dissolved in the alchoholic 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.\textsuperscript{18} 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 possible 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 alchohols were
\( 2 - 5 \times 10^{-4} \) 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.\textsuperscript{11} By heating
the reaction mixture in a sealed ampoule for several hours at 100\textdegree, 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 alchohols 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.\textsuperscript{3,4, cf. also12}
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\textsuperscript{-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.\textsuperscript{2,6,12} The product composition
quantities \( B_{ha} \)' were computed from the expression 2,6,12

\[
B_{ha} = \frac{x}{y} \frac{x_{H_2O}}{x_{Alcoh}} = k_h^o \frac{k_h^o}{k_h^a} K_{ha} \tag{1}
\]

where \( k_h^o \) and \( k_h^a \) 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.\textsuperscript{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

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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.

<table>
<thead>
<tr>
<th>Wt. % MeOH</th>
<th>x&lt;sub&gt;MeOH&lt;/sub&gt;</th>
<th>ν&lt;sup&gt;o&lt;/sup&gt;</th>
<th>x/y</th>
<th>k&lt;sub&gt;h&lt;/sub&gt;</th>
<th>k&lt;sub&gt;m&lt;/sub&gt;</th>
<th>E&lt;sub&gt;h&lt;/sub&gt;</th>
<th>E&lt;sub&gt;m&lt;/sub&gt;</th>
<th>log A&lt;sub&gt;h&lt;/sub&gt;</th>
<th>log A&lt;sub&gt;m&lt;/sub&gt;</th>
<th>E&lt;sub&gt;h&lt;/sub&gt; − E&lt;sub&gt;m&lt;/sub&gt;</th>
<th>B&lt;sub&gt;hm&lt;/sub&gt;</th>
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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.

<table>
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<tr>
<th>Wt. % ETOH</th>
<th>x&lt;sub&gt;ETOH&lt;/sub&gt;</th>
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<th>x/y</th>
<th>k&lt;sub&gt;h&lt;/sub&gt;</th>
<th>k&lt;sub&gt;e&lt;/sub&gt;</th>
<th>E&lt;sub&gt;h&lt;/sub&gt;</th>
<th>E&lt;sub&gt;e&lt;/sub&gt;</th>
<th>log A&lt;sub&gt;h&lt;/sub&gt;</th>
<th>log A&lt;sub&gt;e&lt;/sub&gt;</th>
<th>E&lt;sub&gt;h&lt;/sub&gt; − E&lt;sub&gt;e&lt;/sub&gt;</th>
<th>B&lt;sub&gt;he&lt;/sub&gt;</th>
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<td>12.41</td>
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<td>16.63</td>
<td>12.19</td>
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</tbody>
</table>

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**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.

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<tr>
<th>Wt. % MeOH</th>
<th>x_MeOH</th>
<th>t°C</th>
<th>x/y</th>
<th>k_h</th>
<th>k_m</th>
<th>E_h</th>
<th>E_m</th>
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<td>0.00538</td>
<td>17.68</td>
<td>12.94</td>
<td>11.30</td>
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<td>4.74</td>
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<td>0.0275</td>
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**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.

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<th>E_h</th>
<th>E_e</th>
<th>log A_h</th>
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Table 5. Comparison of the reactivities of some benzene and pyridine derivatives at 25\(^\circ\). 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.

<table>
<thead>
<tr>
<th>Compound</th>
<th>2,4-DNFB</th>
<th>2,6-DNFB</th>
<th>5-NFP</th>
<th>3-NFP</th>
<th>PF</th>
<th>1,2-DNB</th>
<th>1,4-DNB</th>
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<tbody>
<tr>
<td>(k_m^{\circ}(\text{H}_2\text{O}))</td>
<td>0.129</td>
<td>0.275</td>
<td>0.0214</td>
<td>0.0382</td>
<td>700</td>
<td>0.260 \times 10^{-5}</td>
<td>0.0968 \times 10^{-5}</td>
</tr>
<tr>
<td>(k_m^{\circ}(\text{MeOH}))</td>
<td>15.4</td>
<td>5.53</td>
<td>1.98</td>
<td>0.080</td>
<td>\sim 10^{4}</td>
<td>14 \times 10^{-5}</td>
<td>37 \times 10^{-5}</td>
</tr>
<tr>
<td>(k_m^{\circ}(\text{H}_2\text{O})^a)</td>
<td>5.5</td>
<td>5.3</td>
<td>1.1</td>
<td>0.85</td>
<td>\sim 10^{4}</td>
<td></td>
<td></td>
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<tr>
<td>(k_m^{\circ}(\text{EtOH}))</td>
<td>63</td>
<td>9.38</td>
<td>5.52</td>
<td>1.10</td>
<td>\sim 10^{4}</td>
<td>22 \times 10^{-5}</td>
<td>177 \times 10^{-5}</td>
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<tr>
<td>(k_m^{\circ}/k_n^{\circ})</td>
<td>8.1</td>
<td>5.5</td>
<td>1.4</td>
<td>1.1</td>
<td>\sim 10^{4}</td>
<td></td>
<td></td>
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<tr>
<td>(E_n^{\circ}(\text{H}_2\text{O}))</td>
<td>63</td>
<td>20</td>
<td>65</td>
<td>25</td>
<td>18</td>
<td>40</td>
<td>200</td>
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<tr>
<td>(E_n^{\circ}(\text{MeOH}))</td>
<td>16.94</td>
<td>15.39</td>
<td>17.68</td>
<td>16.95</td>
<td>11</td>
<td>23.01</td>
<td>25.56</td>
</tr>
<tr>
<td>(\log A_m^{\circ}(\text{H}_2\text{O}))</td>
<td>13.52</td>
<td>13.70</td>
<td>14.48</td>
<td>14.39</td>
<td>11</td>
<td>22.0</td>
<td>22.6</td>
</tr>
<tr>
<td>(\log A_m^{\circ}(\text{EtOH}))</td>
<td>12.66</td>
<td>13.77</td>
<td>13.88</td>
<td>15.28</td>
<td>11</td>
<td>12.28</td>
<td>12.72</td>
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<tr>
<td>(\log A_m^{\circ}(\text{MeOH}))</td>
<td>11.10</td>
<td>10.80</td>
<td>10.90</td>
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<td>(\log A_e^{\circ}(\text{EtOH}))</td>
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<td>11</td>
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</tr>
<tr>
<td>Ref.</td>
<td>2</td>
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<td>4, 12</td>
<td>5, 6, 12</td>
<td>5, 6, 12</td>
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</tbody>
</table>

\(^a\) 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\(^\circ\) with methoxide ion\(^{14}\) and 1-chloro-2,4-dinitrobenezene reacts 39 times faster than 1-chloro-2,6-dinitrobenezene with methoxide ion at 50\(^\circ\).\(^{16}\)

(iv) If we take \(K_{hn}^{\prime}=4.5\) in methanol-water and \(K_{ne}^{\prime}=0.65\) in ethanol-water mixtures at 25\(^\circ\),\(^{6,12}\) we obtain the values given in Table 5 for the reactivity ratios, \(k_m^{\circ}/k_n^{\circ}\) and \(k_e^{\circ}/k_n^{\circ}\). It is seen that the ratios for 3-NFP are closer

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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 are similar to those for picryl fluoride, although the latter compound reacts about $10^9$ times faster than the former.

(v) Rate constants for alkoxyd 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 $E_h - E_e$ 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.

It has been stated 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 alkoxylaction and dealkoxylaction reactions), and it does not explain the similar $k_0/k_5$ ratios for 2,6-DNFB and 3-NFP. This explanation has been criticized also in connection with amination reactions.

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 defluoroalkoxylation reactions, but not in dealkoxylaction reactions.

REFERENCES


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