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171. Tetsuzo Kato, Harue Hayashi, and Tamiko Anzai: Reactivities of 4-Chloropyridine Derivatives and Their 1-Oxides.

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Rates of reaction of 4-chloropyridine (I), 4-chloro-2-picoline (Ⅱ), 4-chloro-3-picoline (Ⅲ), 4-chloro-2,6-lutidine (Ⅳ), 3-nitro-4-chloro-2,6-lutidine (Ⅴ), 2-trichloromethyl-3-nitro-4-chloro-6-methylpyridine (Ⅵ) and their 1-Oxides with sodium methoxide in methanol have been measured, and rate coefficients, activation energies and entropies of activation were calculated. The order of the reaction rate at 0° found from our experiments was as follows; Ⅵ>Ⅴ-Oxide>Ⅴ>I-Oxide>Ⅱ-Oxide>Ⅲ-Oxide>Ⅳ-Oxide>I>Ⅱ>Ⅲ>Ⅳ.

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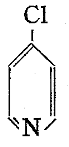
It is well recognized that 4-chloropyridine 1-oxide reacts readily with nucleophilic reagents such as alkoxide, phenoxide, or amine.1) Also, 4-substituent in pyridine is reactive toward nucleophilic reagents and a number of kinetic studies on the reactions have been made.2~5) Liveris and Miller6) reported comparative data for the reactivities of three kinds of chloropyridines and their 1-oxides. However, none of kinetic studies on the reaction of methylpyridine or its 1-oxide have appeared in the literature. Interest in our laboratory has been focused on the comparative data for the reactivities of 4-substituted methylpyridine derivatives and their 1-oxides. In the present paper, we wish to report the reactions of 4-chloropyridine (I), 4-chloro-2-picoline (Ⅱ), 4-chloro-3-picoline (Ⅲ), 4-chloro-2,6-lutidine (Ⅳ), 3-nitro-4-chloro-2,6-lutidine (Ⅴ), 2-trichloromethyl-3-nitro-4-chloro-6-methylpyridine (Ⅵ) and their 1-Oxides (I~Ⅴ-Oxide).7)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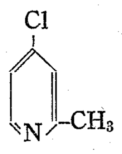
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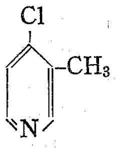
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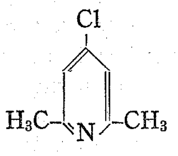
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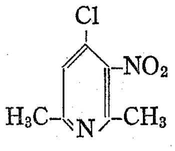
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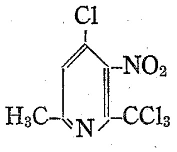
Ⅵ

In the aromatic nucleophilic substitution, the reaction of activated chloro compounds with methoxide was proved to follow bimolelcular reaction mechanism.8) Liveris and Miller6) reported the reactions of chloropyridine and its 1-oxide with an equimolar concentration of sodium methoxide in methanol. However, in the case of methylpyridine the reaction speed was too slow to run in the similar condition of the reaction of 1-oxide, therefore, a large excess of sodium methoxide was used in our investigation except in the cases of 3-nitro compounds (Ⅵ, Ⅴ-Oxide).

[*1] Kita-4, Sendai, Miyagi-ken (加藤鉄三, 林 春江, 安在田美子).
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Experimental

Materials

4-Chloropyridine (I)[9]——This was obtained by the reduction of 4-chloropyridine 1-oxide (I-Oxide)[10] with Raney Ni as a catalyst.[11] The product was unstable, and it was purified by distillation just before using for the kinetic run. b.p_{72} 74°, n_D^{21} 1.4828, picrate m.p. 138～139°.

4-Chloro-2-picoline (II)[12]——This compound was prepared from 4-chloro-2-picoline 1-oxide (II-Oxide)[13] in a similar manner described above. b.p_{100} 100°, n_D^{23} 1.5205, picrate m.p. 175°.

4-Chloro-3-picoline (III)[14]——This was obtained by treating 4-chloro-3-picoline 1-oxide (III-Oxide)[15] with PCl_3 in $CHCl_3$.[16] b.p_{30} 77～78°, n_D^{22} 1.5233, picrate m.p. 155～156.5°.

4-Chloro-2,6-lutidine (IV)[17]——According to the procedure described in the previous paper,[18] 2,6-lutidine 1-oxide was treated with $POCl_3$ to give IV. b.p_{92} 105～106°, $n_D^{20.5}$ 1.5173, picrate m.p. 166°.

3-Nitro-4-chloro-2,6-lutidine (V)[19]——3-Nitro-4-hydroxy-2,6-lutidine was treated with $POCl_3$ by the method reported in the previous paper[19] to give V. m.p. 71～72°.

2-Trichloromethyl-3-nitro-4-chloro-6-methylpyridine (VI)[19]——This was prepared according to the procedure described in the previous paper.[19] m.p. 100°.

4-Chloropyridine 1-Oxide (I-Oxide)[10]——This was obtained by treating 4-nitropyridine 1-oxide with AcCl. m.p. 169°(decomp.), picrate m.p. 146～147°.

4-Chloro-2-picoline 1-Oxide (II-Oxide)[13]——This was prepared by chlorination of 4-nitro-2-picoline 1-oxide with HCl gas in absolute MeOH. b.p_2 120°, HCl salt m.p. 133～134°.

4-Chloro-3-picoline 1-Oxide (III-Oxide)[15]——This was obtained from 4-nitro-3-picoline 1-oxide by the method described in the literature.[20] m.p. 121～122°.

4-Chloro-2,6-lutidine 1-Oxide (IV-Oxide)[21]——This was prepared by treating 4-chloro-2,6-lutidine (IV) with H_2O_2 in AcOH. m.p. 101°.

3-Nitro-4-chloro-2,6-lutidine 1-Oxide (V-Oxide)——3-Nitro-4-chloro-2,6-lutidine (V) (4 g.) was dissolved in a solution of monoperphthalic acid (5.9 g.) in ether. After allowing to stand at room temperature for 24 days, the reaction mixture was washed with 10% K_2CO_3, dried over Na_2SO_4, and condensed. The resulted residue was washed with petroleum ether, and dissolved in benzene. The benzene solution was purified by alumina chromatography. From the $CHCl_3$ eluate 0.6 g. (14%) of V-oxide was obtained, yellow prism (petroleum ether), m.p. 142°. *Anal.* Calcd. for $C_7H_7O_3N_2Cl$ (V-Oxide) : C, 41.43; H, 3.46; N, 13.82. Found : C, 41.62; H, 3.64; N, 13.76. From the petroleum ether and benzene eluate 2.2 g. of V was recovered.

Methanol——Reagent grade MeOH was dried by the magnesium method.[22] This purified MeOH was the solvent for all rate studies, and was also used for preparation of sodium methoxide reagent.

Rate Measurement——Typical procedure was as follows : aliquots of a reaction solution (a mixture of 5 ml. of I-Oxide in absolute MeOH, $1.000\times10^{-3}M/20°$, and 5 ml. of sodium methoxide in MeOH, $2.1042\times10^{-2}M/20°$; concentrations of I-Oxide and methoxide at bath temperature (40°) were 0.04886M and 1.02824 M, respectively) were sealed in ampoules and the ampoules were immersed, all at once, in a thermostat adjusted to 40±0.1°. After the thermostat had returned to the temperature, an ampoule was removed and chilled, and subsequently other ampoules were removed, all times being recorded. Soon after being removed from thermostat, each ampoule was opened and *ca.* 0.9 ml. of conc. HNO_3 was added. After being adjusting pH between 7～10, the solution was titrated with 0.1N $AgNO_3$ (f=1.002) by Mohr's method,[23] and ml. of $AgNO_3$ was recorded. Table I summarizes the above result.

In the case of 2-trichloromethyl-3-nitro-4-chloro-2,6-lutidine (VI), the reaction was carried out in a volumetric flask; that is, VI and sodium methoxide in MeOH were placed in a 50 ml. volumetric flask, and MeOH was added to the mark (concentration of VI and methoxide were 0.02443M and 0.02767M at 29.7°,

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TABLE I. Reaction of 4-Chloropyridine 1-Oxide (I-Oxide) with Sodium Methoxide in MeOH at 40°

Time (min.)	$AgNO_3$ required (ml.)	$\log(a-x)$	Time (min.)	$AgNO_3$ required (ml.)	$\log(a-x)$
8	1.192	0.57955	40	3.332	0.21958
16	1.930	0.48572	48	3.610	0.13988
24	2.530	0.39094	56	3.880	0.04532
32	2.978	0.30363	∞	4.990	

Initial concentration of I-Oxide, 0.04886M; initial concentration of OCH_3^-, 1.02824M; volume of each sample, 10.232 ml.; concentration of $AgNO_3$, 0.1N(f=1.002). From this data k_1 and k_2 were obtained as 2.535×10^{-2} sec^{-1} and 4.109×10^{-4} L·mole^{-1}·sec^{-1}, respectively. In another run k_1 and k_2 were obtained as 2.496×10^{-2} and 4.046×10^{-4}, respectively. The mean value was listed in Table II.

respectively). The solution was shaken thoroughly and immersed in a thermostat. After the thermostat had returned to the temperature, 5 ml. of aliquot was pipetted and quenched. Subsequently, other aliquots were pipetted at diffinite intervals, and all times were recorded. Titration was carried out potentiometric titration method.

Rate Calculations——Rate coefficients were calculated from the expression $\log a-\log(a-x)=\frac{1}{2.303}k_1\cdot t$, $k_2=k_1/b$ (where a and b are initial concentration of the chloro compound and sodium methoxide, respectively, and x is the concentration of the product at time t). Fig. 1 shows the plot of $\log(a-x)$ *vs.* t and the plots were linear. The slope of the line was determined by the method of least squares and the first-order rate coefficient was obtained as 2.5351×10^{-2}/sec. This first-order rate coefficient was divided by the concentration of sodium methoxide, b, to give the second-order rate coefficient k_2 as 4.109×10^{-4} L·mole^{-1}·sec^{-1}. In this experiment, the reaction proceeded to 50% at 27.33 min.

In the case of Ⅵ and V-Oxide, rate coefficients k_2 were calculated according to the literature reported by Liveris and Millers.[6]

Arrehenius activation energy, $\Delta E^{\ddagger}$, was calculated from the expression: $\log k=\log A-1/2.303R\cdot\Delta E^{\ddagger}\cdot1/T$. In Fig. 2, the plots of $\log k$ *versus* $1/T$ are shown. The slope of this line $(1/2.303R\cdot\Delta E^{\ddagger})$ was calculated by the method of least squares and $\Delta E^{\ddagger}$ was obtained as 19.3 kcal·mole^{-1} (lit.,[6] 19.0 kcal·mole^{-1}). From the above expression, rate constants at 0°, 50° and 100° were calculated as 4.39×10^{-6}, 1.07×10^{-3} and 5.99×10^{-2} L·mole^{-1}·sec^{-1}, respectively (lit.,[6] 4.44×10^{-6}(0°), 1.00×10^{-3}(50°), 5.27×10^{-2}(100°) L·mole^{-1}·sec^{-1}). The entropy of activation, $\Delta S^{\ddagger}$, was calculated from the standard equation: $\Delta S^{\ddagger}=2.303R\left(\log\frac{hk}{\kappa T}+\frac{\Delta E^{\ddagger}-RT}{2.303RT}\right)$, to give -14.9 cal·deg^{-1}·mole^{-1} (lit.,[6] 15.6 cal·deg^{-1}·mole^{-1}).

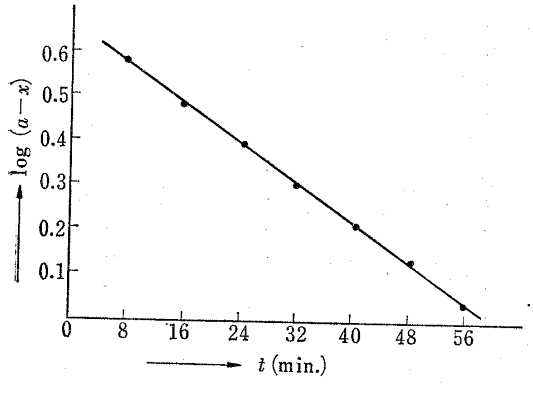

Fig. 1. An Example of the Rate Measurement by Mohr's Titration Method, Reaction of 4-Chloropyridine 1-Oxide (I-Oxide) with Sodium Methoxide at 40° (Table I)

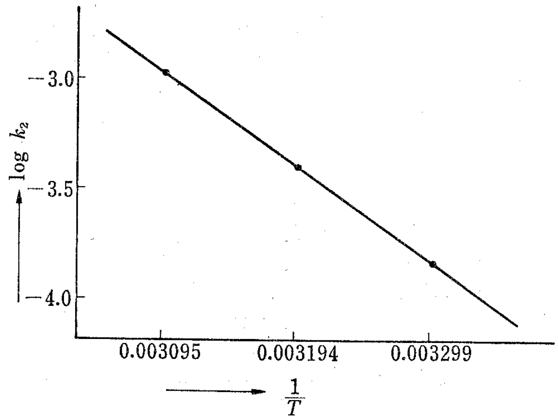

Fig. 2. Plot of $\log k_2$ against $1/T$, Reaction of 4-Chloropyridine 1-Oxide (I-Oxide) with Sodium Methoxide

Results and Discussion

Rate measurements are summarized in Table II, and although in the case of 4-chloropyridine (I) there remained some differences from those reported by Liveris and Millers,6) the summary of the derived parameters are shown in Table III. As shown in Table III, 2-trichloromethyl-3-nitro-4-chloro-6-methylpyridine (VI) reacted more 4×10^6 times faster than 4-chloro-2,6-lutidine (IV), and the order of the reaction rate at 0° found from our study was as follows : VI>V-Oxide>V>I-Oxide>II-Oxide>III-Oxide>IV-Oxide>I>II>III>IV. All activation energies and the entropies of activation fall in the range 16.8 to 23.3 kcal·mole^{-1} and −12.5 to 20.5 cal·deg^{-1}·mole^{-1}, respectively.

Table II. Rate Coefficients found for Reactions with Sodium Methoxide in MeOH

4-Chloro Compound	k_2 (L·mole^{-1}·sec^{-1})			
I	1.25×10^{-4} (89.6°)	2.74×10^{-4} (99°)	5.84×10^{-4} (109°)	1.25×10^{-3} (119.8°)
II	9.63×10^{-5} (99°)	2.44×10^{-4} (109°)	5.00×10^{-4} (119.8°)	
III	9.12×10^{-5} (109°)	2.11×10^{-4} (119.8°)	4.52×10^{-4} (130°)	
IV	1.42×10^{-4} (120°)	2.98×10^{-4} (130°)	5.93×10^{-4} (140°)	
V	2.27×10^{-4} (20.5°)	4.14×10^{-4} (25.2°)	6.94×10^{-4} (31.2°)	1.08×10^{-3} (35.2°)
VI$^{a)}$	1.58×10^{-3} (0.1°)	1.42×10^{-2} (21.3°)	3.22×10^{-2} (29.7°)	
I-Oxide	1.50×10^{-4} (30.1°)	4.08×10^{-4} (40°)	1.08×10^{-3} (50°)	
II-Oxide	1.68×10^{-4} (50°)	4.17×10^{-4} (60°)	9.88×10^{-4} (70°)	
III-Oxide	1.89×10^{-4} (50°)	4.75×10^{-4} (60°)	1.27×10^{-3} (70°)	
IV-Oxide	6.95×10^{-5} (60°)	1.72×10^{-4} (70°)	4.15×10^{-4} (80°)	
V-Oxide$^{a)}$	2.84×10^{-3} (19.9°)	7.33×10^{-3} (29.9°)	1.80×10^{-2} (39.4°)	

a) Reaction was carried out with equimolar concentration of chloro compound and sodium methoxide according to the procedure described in the literature.6)

Table III. Calculated Rate Coefficients and Some Derived Parameters for Reactions with Methoxide in MeOH

4-Chloro Compound	k_2 (L·mole^{-1}·sec^{-1}) 0°	50°	100°	$\Delta E^{\neq}$ kcal·mole^{-1}	$\Delta S^{\neq}$ cal·deg^{-1}·mole^{-1}
I	6.81×10^{-9} $(6.59\times10^{-10})^{a)}$	3.22×10^{-6} $(8.91\times10^{-7})^{a)}$	2.91×10^{-4} $(1.67\times10^{-4})^{a)}$	21.6 (25.2)$^{a)}$	−19.3 (−10.4)$^{a)}$
II	1.30×10^{-9}	8.91×10^{-7}	1.06×10^{-4}	22.9	−17.8
III	4.35×10^{-10}	3.34×10^{-7}	4.33×10^{-5}	23.3	−18.5
IV	3.79×10^{-10}	2.55×10^{-7}	3.00×10^{-5}	22.8	−20.5
V	2.71×10^{-5}	4.01×10^{-3}	1.22×10^{-1}	17.5	−18.2
VI	1.56×10^{-3}	1.86×10^{-1}	6.13	16.8	−12.5
I-Oxide	4.39×10^{-6} $(4.44\times10^{-6})^{a)}$	1.07×10^{-3} $(1.00\times10^{-3})^{a)}$	5.99×10^{-2} $(5.27\times10^{-2})^{a)}$	19.3 (19.0)$^{a)}$	−14.9 (−15.6)$^{a)}$
II-Oxide	6.56×10^{-7}	1.67×10^{-4}	9.66×10^{-3}	19.4	−18.1
III-Oxide	5.42×10^{-7}	1.86×10^{-4}	1.34×10^{-2}	20.5	−14.7
IV-Oxide	6.73×10^{-8}	2.60×10^{-5}	2.04×10^{-3}	20.9	−17.3
V-Oxide	3.30×10^{-4}	4.47×10^{-2}	1.62	17.2	−13.9

a) Values from the literature reported by Liveris and Millers.6)

Ratios of k_2 values of each two compounds at 0°, 50° and 100° were calculated, which are shown in Table IV.

It is well recognized that the methyl group in benzene ring deactivates aromatic nucleophilic substitution reaction. As shown in Table IV, pyridine (I) and its 1-oxide were faster than their methyl derivatives, respectively. On the other hand, the methyl group at the 2-position in the pyrididine corresponds to the meta substituent for the 4-chloro group. Therefore, Hammett rule would be available for pyridine, 2-picoline, 2,6-lutidine or their 1-oxides. Fig. 2 and 3 are the Hammett plots in which $\log k_2$ of pyridines (I, II and IV) and their 1-oxides are plotted against sigma values[24] at 50°, and the points fall nearly on a line.

TABLE IV. Ratios of Rate Coefficients at 0°, 50° and 100°

Compounds	Ratio (k_2/k_2)		
	0°	50°	100°
I/II	5.2	3.6	2.8
I/III	15.7	9.6	6.7
II/IV	3.4	3.5	3.5
I/IV	18.0	12.6	9.7
I-Oxide/II-Oxide	6.7	6.4	6.2
I-Oxide/III-Oxide	8.1	5.7	4.5
II-Oxide/IV-Oxide	9.8	6.4	4.7
I-Oxide/IV-Oxide	65.2	41.1	29.4
I-Oxide/I	645	332	206
II-Oxide/II	505	188	92
III-Oxide/III	1246	557	309
IV-Oxide/IV	177	102	68
V-Oxide/V	15	14	13
V-Oxide/IV-Oxide	4900	1700	780
V/IV	5.8×10^4	1.3×10^4	4100

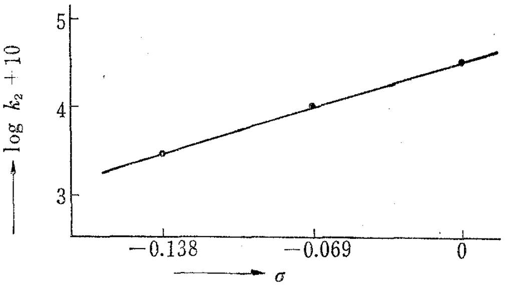

Fig. 3. Plot of Sigma against $\log k_2$ from Reactions of 4-Chloropyridine (I), 4-Chloro-2-picoline (II) and 4-Chloro-2,6-lutidine (IV) with Sodium Methoxide in MeOH at 50°

Sigma values used as follows; for m-CH_3, −0.069; for m,m'-di-CH_3, −0.138.[24]

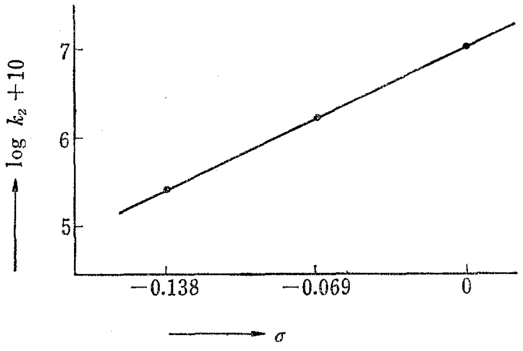

Fig. 4. Plof of Sigma against $\log k_2$ from Reactions of I-Oxide, II-Oxide and IV-Oxide at 50°

As mentioned in the biginning of this paper, the 1-oxide group accelerates the nucleophilic substitution reaction. As shown in Table IV, our results are well in agreement with this fact. On the other hand, though the details of the mechanism are obscure for the present, the 1-oxide group is also realized as one which facilitates the electrophilic substitution reaction.[1,24] As shown in Table IV, ratios are at variance at different temperatures; that is, as temperature rised the ratio decreased. This result suggests that the 1-oxide function deactivates nucleophilic substitution in higher tempera-

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ture, namely, −M effect (electron releasing) of the 1-oxide would be expected in higher temperature.

When the nitro group is present at 3-position of 4-chloro-2,6-lutidine (Ⅳ), the rate ratio increased tremendously (5.76×10^4 times at 0°). However, comparing with the accelerating power of N-oxide group of pyridine or methylpyridine series (Ⅰ~Ⅳ) that of 3-nitro-2,6-lutidine is not so strong (*ca.* 15 times). Furthermore, the rate ratios of Ⅴ-Oxide and Ⅴ at 0°, 50° and 100° were almost the same (15~13 times).

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