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CHLORINE-ISOTOPIC EXCHANGE BETWEEN LITHIUM CHLORIDE AND SUBSTITUTED 2-CHLOROPYRIDINE IN HOMOGENEOUS SOLUTION

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Abstract—The kinetics of chlorine-isotopic exchange between lithium chloride-36 and cyano- and nitro-substituted 2-chloropyridines were measured in sulpholane, acetone or methanol solution. Activating effects of *ortho*-nitro and *ortho*-aza substitution are compared: a nitro-group is 50 × as activating as the aza-group in the *p*-nitrochlorobenzene system, whereas it is the aza-function which is 3 times as activating as the nitro group in the *o*-nitrochlorobenzene system. The effect of Me substituents placed *ortho* to an activating nitro-group was studied by comparing 2-chloro-3-cyano-5-nitropyridine and its 6-methyl- and 4,6-dimethyl-derivatives.

Previously we have studied the kinetics of chlorine-isotopic exchange in stable homogeneous solution between lithium chloride-^{36}Cl and monochloro-,[1,2] dichloro-,[3] and tetrachloro-benzene[4] derivatives activated by one or more nitro groups. The work here presented deals with the reaction of some derivatives of 2-chloropyridine activated by cyano or nitro groups; some of the compounds were selected because of the availability of kinetic data from related nucleophilic reactions.[5–7]

RESULTS AND DISCUSSION

Kinetics for the chlorine-isotopic exchange reactions of seven derivatives of 2-chloropyridine were determined in sulpholane, acetone or methanol solution. Computed rate constants and activation parameters are given in Table 1. Rate constants have been computed for reactions in sulpholane solution, and are compared with data obtained earlier[2] in that solvent for nitro-substituted chlorobenzenes, in order to assess the effect on rate of substituents. Two derivatives of 4-chloropyridine could not similarly be studied; 4-chloro-3-nitropyridine proved too unstable, and 4-chloro-3,5-dinitropyridine too sensitive to water (Experimental).

Solvent effects. Rates for the exchange reactions increase in the sequence methanol < sulpholane < acetone, in agreement with earlier work.[2,3] The magnitude of the solvent effect, however, varies with the substrate. Thus, for acetone/sulpholane

Table 1. Activation parameters, and computed rate constants at 298.15K, for the chlorine-isotopic exchange between LiCl and substituted 2-chloropyridines or chlorobenzenes in acetone, methanol or sulpholane solution

No	Substrate	Solvent	k_2(298.15K) ($dm^3mol^{-1}s^{-1}$)	Rel.Rate[a] (sulpholane, 298.15K)	$\Delta H^{\ddagger}$ ($kJ\ mol^{-1}$)	$\Delta S^{\ddagger}$ ($JK^{-1}mol^{-1}$)
		(a) substituted 2-chloropyridine				
	3-cyano-	sulpholane	5.07×10^{-8}	8.56×10^{4}	107.6	-24
	3-cyano-5-nitro	methanol	3.85×10^{-6}		73.3	-103
	3-cyano-5-nitro	acetone	4.91×10^{-3}	6.1×10^{8} [b]	73.8	-42
	3-cyano-6-methyl-5-nitro	sulpholane	3.73×10^{-5}	6.30×10^{7}	91.6	-22
	3-cyano-6-methyl-5-nitro	acetone	5.11×10^{-4}		71.4	-67
	3-cyano-4,6-dimethyl-5-nitro	acetone	1.13×10^{-6}	1.4×10^{5} [b]	76.4	-103
	3-nitro	sulpholane	2.16×10^{-7}	3.65×10^{5}	96.6	-48
	5-nitro	sulpholane	1.21×10^{-8}	2.04×10^{4}	110.2	-27
	3,5-dinitro	methanol	1.64×10^{-5}	2.59×10^{9}	68.5	-107
		(b) substituted chlorobenzene				
	2-nitro	sulpholane	5.92×10^{-13}	1.00	126.8	-53
	4-nitro	sulpholane	3.77×10^{-13}	7.37×10^{-1}	138.4	-18
	2,4-dinitro	sulpholane		1.0×10^{6} [b]		

and 1,3-dichloro-4,6-dinitrobenzene a ratio = 10.7 had been found.[3] For 2-chloro-3-cyano-6-methyl-5-nitropyridine the ratio = 13.7 (Table 1). Errors incurred in extrapolating rates from another solvent to sulpholane (Set Nos 3 and 6) should not be serious, however, because effects on rates by substituents are very much greater.

The exchange reactions conducted in sulpholane solution are characterised by relatively high entropies of activation ($\Delta S^{\ddagger} = -22$ to $-48\,J\,K^{-1}\,mol^{-1}$), whilst for methanol solutions lower values obtain ($\Delta S^{\ddagger}$ $-100\,J\,K^{-1}\,mol^{-1}$). 2-Chloro-3-cyano-5-nitropyridine reacts *ca* 1300 times as fast in acetone as in methanol solution; this difference in rate is seen to be due solely to changes in the entropy of activation ($\Delta\Delta S^{\ddagger} = +60\,J\,K^{-1}\,mol^{-1}$). For the reactions of 2-chloro-3-cyano-6-methyl-5-nitropyridine (Set Nos. 4 and 5) a change of solvent produces more subtle changes in the activation parameters.

The rate increase must be due to a decrease in $\Delta H^{\ddagger}$ (of *ca.* $20\,kJ\,mol^{-1}$), and would have been greater but for an accompanying substantial decrease in $\Delta S^{\ddagger}$ (of *ca* $45\,J\,K^{-1}\,mol^{-1}$).

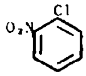
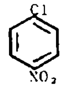
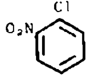
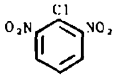
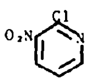
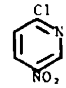
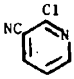
Substituent effects. The effects of substituents derived from data in Table 1 and earlier work,[2,3] on the rate constants of isotopic chloride exchange of several substituted 2-chloropyridines and chlorobenzenes, are summarised in Table 2. Substitution by an aza-function, by a 2-cyano, by a 2- or a 4-nitro substituent, all cause activation of the chloroaryl group by factors within the range 2×10^3–2×10^6. Small rate differences ($< 40\%$),[3] due to the effects of changing concentrations of the substrate or lithium chloride, could therefore be neglected.

By assuming additivity of substitutent effects the rate constants (k at 298.15K in sulpholane) for the parent molecules could be estimated, viz. for chlorobenzene $\sim 4.3 \times 10^{-18}\,dm^3\,mol^{-1}\,s^{-1}$, and for 2-chloropyridine $\sim 1.7 \times 10^{-12}\,dm^3\,mol^{-1}\,s^{-1}$. This would correspond to reaction $t_{1/2}$'s of 9×10^{10} and 2×10^5 years, respectively.

With 4-nitro-1-chlorobenzene and 2,4-dinitro-1-chlorobenzene an *ortho*-nitro substituent is more effective than an *ortho*-aza function, by factors of *ca* 50 × and 25 ×, respectively, but for 2-nitro-1-chlorobenzene it is conversely the *ortho*-aza function which is 3 × more rate-enhancing. This discrepancy may be more apparent than real, since, with the less reactive haloarenes it had proved necessary to extrapolate rates across a wide temperature gap. Earlier comparisons of the effect of these substituents on other types of nucleophilic substitution gave rate ratios for 2-nitro-1-chlorobenzene/2-chloropyridine (with ethoxide in ethanol at 20°) = 82,[8] for 1-chloro-2,4-dinitrobenzene/2-chloro-5-nitropyridine (with pyridine in ethanol at 55°) = 5.6,[9] and for the same derivatives (with primary aromatic amines, in ethanol, at 55°) = 28–30.[9]

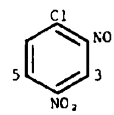
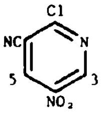
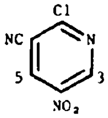
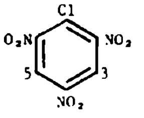
As expected from the general polar effects as susbstituents,[10] a nitro-group placed *ortho* to chlorine

Table 2. Effect of substitution by cyano- or nitro-groups, or aza-function, on rate constants of chlorine-isotopic exchange reactions, in sulpholane solution at 298.15K, of derivatives of chlorobenzene and 2-chloropyridine

	Rate enhancements observed, on substitution by			
Substrate[a]	4-NO$_2$	2-NO$_2$	2-aza	2-CN
	1.0×10^6 [b]	1.37×10^5 [b]	3.94×10^5 [b]	3.22×10^4 [b]
	1.0×10^6	1.37×10^5	3.65×10^5	
	-	1.56×10^6	3.20×10^4	
	-	6.46×10^4 [c]	2.59×10^3	
	2.16×10^6 [c]	-	-	-
	7.10×10^3	-	-	-
	-	1.27×10^5		2.97×10^4
	7.07×10^3	-	-	-

[a] Numbering the chloro-group at 1-position [b] extrapolated [c] in acetone solution

Table 3. The effect of *meta*-methyl substitution on the rates of nucleophilic substitution of activated aromatic chloro-compounds

	Relative rates				
System studied[a]					
Nucleophilie	piperidine[b]	aniline[c]	aniline[d]	LiCl[e]	LiCl[f]
stituent					
H	1.00	1.00	1.00	1.00	1.00
-Me	1.23×10^{-3}	2.06×10^{-1}	2.70×10^{-1}	1.03×10^{-1}	5.27×10^{-3}
,5-Me_2			3.72×10^{-3}	2.3×10^{-4}	1.28×10^{-6}

loro-group at 1-position [b] In ethanol, at 30°C (Ref 12) [c] In sec-butanol at 20°C (Ref 7) [d] In methanol at 30°C (Ref 5)

n acetone at 25°C (this work) [f] In acetone at 25°C (Ref 2).

proved *ca* 4x more activating than a cyano-group, for the exchange reactions of 2-chloro-5-nitropyridine.

Effect of methyl substitution. The influence of Me substitution on the reactivity of 2-chloro-3-cyano-5-nitropyridine was studied in acetone solution. Substitution of a Me group at the 6-position resulted in a 10-fold rate reduction; a second Me group, at the 4-position, produced a further reduction in rate by a factor of 450. Since the polar effects (+ I) of Me groups *meta-* to the reaction site are likely to be small,[5] the effects observed here must have a different origin, viz. they constitute a secondary steric effect. A Me placed *ortho* to a nitro group is likely to cause a substantial rotation of that group away from the aromatic plane, to avoid strain arising from non-bonded interactions. A nitro group *ortho* to a Cl, similar sterically to a Me, has been shown[11] to have an effective conformational angle of *ca* 40 . Mesomeric activation of the nucleophilic substitution will thus be substantially reduced. A second *ortho*-Me group will cause further rotation of the nitro group, probably to an orthogonal position,[2] where the mesomeric contribution of its activation will have been reduced to zero.

The steric effect of *meta*-Me groups on nucleophilic substitutions of Cl-groups, activated by *ortho* or *para* nitro groups, is summarised in Table 3. The rate-lowering effect of a Me group is seen to be much more powerful in systems where two nitro groups are affected directly, than in the reactions of the pyridine derivatives where only one activating group, the *p*-nitro, is directly modified by Me substitution. A second Me group, similarly, is much more powerfully deactivating in the case of 1-chloro-2,4,6-trinitrobenzene.[2]

Reductions in rate both in the 1-chloro-2,4-dinitrobenzene and 1-chloro-2,4,6-trinitrobenzene systems are caused by major increases in enthalpies of activation ($\Delta H^{\ddagger}$) without a significant change in entropies of activation ($\Delta S^{\ddagger}$). In the present system, however, the rate reductions are due essentially to progressive decreases in $\Delta S^{\ddagger}$, of 25 and 36 J K^{-1} mol^{-1}, respectively, whilst there are only minor variations ($<5\%$) in $\Delta H^{\ddagger}$.

One may use the fact of these reactions being isoenthalpic to calculate the contributions of the invariant and variable components of the electronic mechanisms to the rate-activation caused by the nitro group, and the rate-reduction caused by the Me group. For a constant $\Delta H^{\ddagger}$ the energy differences, between the initial states and the transition states, remain the same; therefore, one can assess the effect of changes in $\Delta S^{\ddagger}$ of the substituents by examining the factors which operate on the structure of the substrate itself.

It may be assumed that a 4-nitro substituent activates the Cl group in 2-chloro-3-cyanopyridine by an inductive effect (I_{NO_2}) and a mesomeric effect (M_{NO_2}), working in concert. The former is taken as constant, whilst the contribution of the M_{NO_2} effect will be fully operational only in the case of a coplanar nitro group, i.e. in the absence of *ortho*-Me's, and will in their presence be reduced according to the conformational angle (θ) between the nitro group and the plane of the pyridine ring. The relationship normally employed[13] involves the term $\cos^2\theta$, and this is used here. It is further assumed that the (deactivating) electronic effect (Me) of the first and second Me substituents will be the same. We can then use expression (I)

$$\frac{k(\text{2-chloro-3-cyano-}x\text{-methyl-5-nitro})}{k(\text{2-chloro-3-cyano-pyridine})} = \frac{I_{NO_2} + M_{NO_2}\cdot\cos^2\theta}{Me^n} \tag{I}$$

(where n = number (0, 1, 2) of Me substituents) to provide us with three equations in three unknowns, which can therefore be derived. For $\theta = 40°$ (see above) the values obtained for $I_{NO_2} = 52$, $M_{NO_2} = 7070$, and $Me = 5.7$, represent their contributions to the activation (NO_2)/deactivation (Me) produced by these substituents, acting through changes in $\Delta S^{\ddagger}$ on the reactivity of the 2-chloro-3-cyanopyridine system. For a somewhat altered angle θ ($\pm 5°$) one

Table 4. Experimental rate constants for the chlorine-isotopic exchange between substituted 2-chloropyridines(A) and lithium chloride (B)

Set No.[a]	10^2[A] [b] (mol dm^{-3})	10^2[B] [b] (mol dm^{-3})	$10^4 k_2$ (dm^{3}mol^{-1}s^{-1}) [c]
1	3.13(0.081)	2.48(0.058)	4.68(375.2), 7.62(380.3), 12.5(386.8), 30.7(396.6), 57.6(403.8)
2	3.51(0.018)	2.43(0.005)	0.342(321.1), 0.489(325.2), 0.649(328.5)
3	3.63(0.028)	2.43(0.020)	5.08(278.5), 10.2(283.1), 17.1(288.1), 31.9(293.1), 47.6(298.1), 77.1(303.
4	3.01(0.009)	2.30(0.009)	6.96(323.0), 19.1(332.8), 40.7(340.1)
5	2.99(0.041)	2.07(0.023)	3.61(295.6), 6.82(300.1). 11.3(305.8), 18.5(312.1), 30.4(316.1), 41.7(320.
6	3.36(0.019)	2.41(0.019)	0.0294(308.4), 0.0559(313.0), 0.0775(316.1), 0.0862(318.2), 0.0892(319.4) 0.0953(320.6)
7	3.09(0.042)	2.39(0.028)	15.0(382.9), 32.2(392.4), 67.9(402.4)
8	3.43(0.011)	2.42(0.045)	2.73(382.8), 4.30(387.6), 7.73(393.3), 11.7(399.1), 19.6(404.1), 25.5(409.
9	3.16(0.016)	2.44(0.021)	0.460(309.4), 0.728(314.4), 0.964(317.3), 1.15(320.3), 1.47(323.4), 1.94(3

[a] see Table 1 [b] standard deviation in parentheses [c] Temperature, K, in parentheses

observes a minute variation for M_{NO_2}: $\pm 0.2\%$, and greater changes for I_{NO_2} ($\pm 33\%$), and Me ($\pm 15\%$). The magnitudes of these electronic effects are not unreasonable, *viz.* that for a 4-nitro substituent the contribution of $-M_{NO_2}$ is here far more important than that of $-I_{NO_2}$, and that $-I_{NO_2}$ is greater than $+I_{Me}$ by a factor of *ca* 9.

EXPERIMENTAL

General. Mps are uncorrected. UV light absorption data were obtained for solns in MeOH and molar extinction coefficients (ε) given in parentheses are in units of m^2 mol^{-1}. PMR spectra were obtained for solns in tetrachloromethane.

Materials. 2-Chloro-3-nitropyridine[14] had m.p. 100° (lit.[9] m.p. 102°) UV max at 208 (1365), 240 (333) and 274 nm (250); PMR τ 2.56 (t, 5-*H*), 1.80 (dd, 4-*H*), 1.41 (dd, 6-*H*), $J_{4,5}$ 7.9 Hz, $J_{4,6}$ 1.9 Hz, $J_{5,6}$ 4.6 Hz. 2-Chloro-5-nitropyridine[9] had m.p. 107–108° (lit.[6] m.p. 107.5–108°); UV max at 209 (1133), 253 (778), and 279 nm (767); PMR τ 2.56 (d, 3-*H*), 1.68 (dd, 4-*H*), 0.94 (d, 6-*H*), $J_{3,4}$ 8.5 Hz, $J_{4,6}$ 2.8 Hz. 2-Chloro-3,5-dinitropyridine[14] had m.p. 63–64° (lit[14] m.p. 63–64°); UV max at 210 (1438), 230 (1063), 253 (850) and 287 nm (500); PMR τ 1.15 (d, 4-*H*), 0.72 (d, 6-*H*), $J_{4,6}$ 1.5 Hz. 4-Chloro-3-nitropyridine, prepared from 3-nitro-4-pyridone,[15] was a pale yellow solid, m.p. *ca* 30° (lit.[9] m.p. 34°), which underwent self-condensation to an insoluble orange product (see Ref. 16). 4-Chloro-3,5-dinitropyridine[14] had m.p. 68 68.5° (lit.[14] m.p. 68°); PMR τ 0.90 (s, 2- and 6-*H*). It rapidly underwent hydrolysis to the pyridone, m.p 313 315° (lit.[17] m.p. 324 325°). 2-Chloro-3-cyanopyridine[18] had m.p. 107° (lit.[5] m.p. 107 107.5°); UV max at 205 (880), 222 (860), 226 (860), 274 (315) and 282 nm (255); PMR τ 2.56 (t, 5-*H*), 1.88 (dd, 4-*H*), and 1.28 (dd, 6-*H*), $J_{4,5}$ 7.8 Hz, $J_{4,6}$ 1.9 Hz; $J_{5,6}$ 4.8 Hz. 2-Chloro-3-cyano-5-nitropyridine[5,19] had m.p. 121–122° (lit.[6] 122–123°); UV max at 218 (1740), 253 (800), and 283 nm (460); PMR τ 1.34 (d, 4-*H*) and 0.74 (d, 6-*H*), $J_{4,6}$ 2.8 Hz. 2-Chloro-3-cyano-6-methyl-5-nitropyridine[20] had m.p. 102–103° (lit.[7,20] m.p. 98–99°); UV max at 217 (2154), 257 (851) and 288 nm (443); PMR τ 1.33 (s, 4-*H*), 7.00 (s, C*H*$_3$). 2-Chloro-3-cyano-4,6-dimethyl-5-nitropyridine had m.p. 112–113° (lit.[5] m.p. 113–114°); UV max at 211 (2250) and 280 nm (233).

Kinetics. The kinetics were determined by the "direct" method, described earlier.[1,21] The rate constants obtained are given in Table 4, and activation parameters in Table 1.

Calculation of substituent effects. For an angle $\theta = 40°$, we have three equations, as represented by Ia, b, c.

$$7.126 \times 10^3 = (I_{NO_2} + \cos^2 0 \,.M_{NO_2})/1 \tag{Ia}$$

$$7.360 \times 10^2 = (I_{NO_2} + \cos^2 40 \,.M_{NO_2})/Me \tag{Ib}$$

$$1.6238 = (I_{NO_2} + \cos^2 90 \,.M_{NO_2})/Me^2 \tag{Ic}$$

Solving, one obtains: $I_{NO_2} = 51.9$, $M_{NO_2} = 7074$, Me = 5.65

Alternatively, for an angle $\theta = 35°$, one obtains: $I_{NO_2} = 69.2$, $M_{NO_2} = 7057$, Me = 6.53; and for $\theta = 45°$, one obtains: $I_{NO_2} = 38.5$, $M_{NO_2} = 7088$, and Me = 4.87.

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