The Deactivating Effect of a *meta*-Methoxy Group in the Methoxydechlorination of Pyridine and Pyrimidine Derivatives (1)

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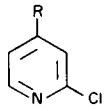
Reactivity data and the activation parameters for the methoxydechlorination of some 2-chloro-4-*R*-pyridines and 4-chloro-6-*R*-pyrimidines have been determined. A methoxy group *meta* with respect to the reaction site is found to be deactivating as already observed in the quinoline series. This gives further support to the hypothesis that in *N*-heteroaromatic systems a conjugative interaction of an electron-releasing substituent with the aza group (s) is a factor in modifying the nucleophilic reactivity as predicted by Hammett's σ_m values.

A. Introduction.

In the methoxydechlorination of 2- and 4-chloroquinoline the alkoxy groups which are in *meta* positions with respect to the reaction center have a distinctly deactivating effect (4). This deactivation is a case where the conjugative effect is greater than the inductive effect and is peculiar because it is in contrast with the positive sign of σ_m (5). It appears to be general because it has been observed also in other reactions of quinoline derivatives (6) and for other substituents of the same electronic type. It can be attributed to an enhancement of the conjugative effect (4,7) as caused by the superimposition of two different factors, one due to the difference in aromatic character of a fused-ring system ("anellation") compared to a six-membered ring and the other to a direct conjugative interaction between the substituent and the aza group which are *ortho* or *para* to each other, with a consequent reduction of the electron-withdrawing effect of the nitrogen.

The presence of the first factor seems now a well established fact in the literature. Thus, in several reactions of nonactivated naphthalene systems, inversions with respect to the "benzoic" reactivities are observed when the methoxy group is located in a position of the nonconjugative type, whether homonuclear or heteronuclear with respect to the reaction center (8,9,10).

On the other hand, conclusive evidence must be obtained for the second factor and should be sought from the behaviour of the monocyclic heteroaromatic systems. Quantitative data are missing in spite of the fact that in preparative work the reactivity of 4-chloro-6-methoxypyrimidine (11) is known to be relatively low and the gradual replacement of the halogen atoms by methoxy groups in the case of 2,4,6-trichloropyrimidine (12) and 2,4,6-tribromopyridine (13) is found to be increasingly difficult. For this reason we now report on a study of the kinetics of methoxy dechlorination in methyl alcohol of some chloropyridines and chloropyrimidines, I and II, in which R (H or CH_3, Cl, OCH_3) is located in the *meta* position with respect to the reaction center and in a conjugative position with respect to the aza group.



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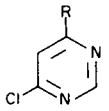

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B. Results and Discussion.

In agreement with preceding observations (14a, 14b) the reactions of the compounds studied give the expected products and follow regular second order kinetics with the exception of 2-chloro-4-methoxypyridine for which preliminary kinetic results had displayed an abnormal course, consisting of a downward curvature of the second order plot. Product analysis shows that the expected product of nuclear substitution is accompanied by 2-methoxy-4-pyridone, which probably results from a subsequent demethylation reaction brought about by the methoxide reagent. The chloride ion displacement is then slowed down by the decreased concentration of the reagent which is used up in the side reaction.

Dealkylation reactions of this kind are well known in the case of alkyl nitroaryl ethers (15), while information for alkyl heteroaryl ethers is scarce. The dealkylation reaction appears to favour the gamma position. Thus, 2-methoxy-4-chloropyridine undergoes the methoxydechlorination reaction by regular second order kinetics; also, 2,4-dimethoxypyridine is demethylated by methoxide ion mainly at the gamma position. In the quinoline series, however, there are examples of preferred demethylation at the alpha position with other nucleophilic reagents (16, 17).

TABLE

Kinetic Data for the Methoxy dechlorination Reaction in Methanol of some 2-Chloro-4-*R*-pyridines (at 120°) and 4-Chloro-6-*R*-pyrimidines (at 15°)

Compound	R	$k_2 \times 10^3$ (a)	k/k_o	E_{act} (b)	log A (a)	$\triangle H^*$ (b)	$-\triangle S^*$ e.u.
2-Chloropyridine	4–Cl	410 (c)	34.7	23.2	10.5	22.5	12.7
	4–H	11.8 (d)	1	29.6	12.5	28.8	3.89
	4–OCH_3	8.38 (e)	0.71	28.9	12.0	28.1	6.35
4-Chloropyrimidine	6–Cl	5100	16	14.5	10.0	14.0	13.6
	6–H	316 (f)	1	--	--	--	--
	6–CH_3	191	0.60	15.5	9.0	14.9	19.2
	6–OCH_3	8.66	0.027	17.9	9.5	17.3	17.0

(a) Units of k and A are $l \cdot mole^{-1} \cdot sec^{-1}$. (b) Units of E_{act} and $\triangle H^*$ are kcal/mole. (c) Partial rate constant (see Experimental) evaluated from the Arrhenius parameters. (d) Calculated from the Arrhenius parameters and corrected for the statistical factor when necessary. (e) Obtained by the initial rate method (see Experimental). (f) Estimated value (see text).

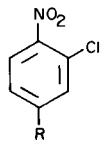
The second order rate constants at one temperature, the relative reactivities and the activation parameters are reported in the Table. The rate constants at other temperatures are reported in the Experimental. The values recorded for 2,4-dichloropyridine are partial rate factors for the substitution reaction at the alpha position. The rate constants for the 2-chloro-4-methoxy derivative were evaluated by the method of initial rates.

In the pyrimidine series (II), because of the instability of 4-chloro-pyrimidine (18), the rate constant for this term (R=H) has been calculated by interpolating the reactivity data of 4,6-dichloro (R=Cl) and 4-chloro-6-methylpyrimidine (R=CH_3) as functions of the σ_m constant (4). The value thus found is 3.2×10^{-3} at 15°. This method of calculation probably involves some error due to the enhanced +R effect of the chloro substituent as bound to the *N*-heteroaromatic system. The error, however, can be neglected for our purposes both because the enhancement is small and because the reactivity of the term with R=H is closer to the derivative with R=CH_3 than to the one with R=Cl.

From the values of the relative reactivities, k/k_o, it is evident that also in the case of aza benzenes the *meta*-methoxy group is deactivating. The effect is notably different in the two series examined, the deactivating factor being just 1.4 in the case of the pyridine series (I), with only one aza group, and 36 in the case of the pyrimidine series (II), with two aza groups. In the first case where the activation energies have been determined for both terms, R=H and R=OCH_3, the effect is found to vary little with temperature because of the small difference in E_a.

In the series of 2-chloroquinoline the situation is in-between the ones now described, but is more similar to that found for the pyridine derivatives, the factor of deactivation being about 4.5.

From the cases above reported, we note a tendency for the reactivity ratio, $k(m\text{-}OCH_3)/k(H)$, to decrease with an increase of reactivity level of the reference substrate. In the corresponding nitro activated substrates it seems that a similar relation holds, since the reactivity ratio, $k(m\text{-}OCH_3)/k(H)$, decreases on going from 2-chloro-4-*R*-nitrobenzene (19,20) to 2,4-dinitro-5-*R*-chlorobenzene (21) even if only in the case of the dinitro derivatives, such a ratio becomes less than one, *i.e.*, the methoxy group is effectively deactivating. A larger number of data related to dinitro derivatives would be desirable. In any case, we note that in the nitro activated substrates III and IV the group R=OCH_3 has less tendency to work as a deactivating substituent than in the corresponding aza activated substrates I and II. This is probably partly due to a steric effect, which may decrease the conjugation of OCH_3 with the nitro group, *ortho* to Cl, in the ground state of the molecule. It is known, in fact (22), that in *o*-chloronitrobenzene, the nitro group makes an angle of about 70° with the aromatic ring.



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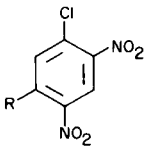

IV

In the transition state, whose structure is presumably close to that of a Meisenheimer adduct (23), the steric compression decreases because of the formation of a tetrahedral carbon atom at the point of attack of the reagent.

It is also worth noting that Bevan et al., (24) have found inversion of the reactivity even in the case of the methoxydefluorination of 3-methoxy-5-nitrofluorobenzene, in which the substituent is not capable of interacting conjugatively with the nitro group. This was explained as a second order effect due to a particularly high sensitivity of the reaction to the charge density at the ring position next to that where the fluoro group is, and it probably involves a leaving group effect as well.

As far as the activation parameters are concerned, we note that for the series of 2-chloropyridine and 2-chloroquinoline (4) the depressing effect on the reactivity caused by the methoxy group is exclusively due to a more negative value of the entropy of activation, the energy of activation being greater for the unsubstituted chloro derivatives. Furthermore, in both series of compounds I and II, the variations of the entropies of activation are relatively large (8.8 and 5.6 entropy units for pyridine and pyrimidine derivatives, respectively). Such cases and others already reported in the literature not only for heteroaromatic derivatives (4, 25) but also for nitro activated aromatic derivatives (20) show that both variations in entropy and in energy of activation can be just as important functions of the electronic structure. These relations, nevertheless, seem to depend on various structural factors, such as the number and nature of activating groups, the nature of the nucleophile, and the solvent.

EXPERIMENTAL

Materials.

4,6-Dichloropyrimidine (Fluka-purum) was repeatedly sublimed at 35° and 0.3 Torr to a m.p. of 66.5-67.5°, lit. (26) m.p. 67°, and was stored at -20°. 4-Chloro-6-methoxypyrimidine was prepared and purified according to Isbecque *et.al.*, (27), m.p. 31.5-32.5°. 4-Chloro-6-methylpyrimidine was obtained by the desulphurisation (28) of 6-methyl-2-thiouracil (Fluka) followed by treatment of the pure 6-methyl-4-pyrimidinone thus obtained with phosphoryl chloride (29). The crude 4-chloro derivative was first distilled at reduced pressure in an empty tube semimicro column according to Rose (30) and the fraction of b.p. 71-71.5° (17 Torr) was subsequently sublimed at 35° and 0.3 Torr, m.p. 35-36°. 2-Chloropyridine (Fluka-purum) was distilled at reduced pressure in a semimicro Todd column (packing: Monel metal); the fraction of b.p. 60.5° (14 Torr), n_D^{25} 1.5302 (14b) was used for the kinetic measurements. 2,4-Dichloropyridine was obtained from 4-nitropyridine 1-oxide (Fluka) according to Itai (31); the crude product was first distilled at reduced pressure in a Rose column (30) and the fraction of b.p. 83-86° (18 Torr) was collected. This was further fractionated to give a fraction, b.p. 74-76° (12 Torr). Some remaining impurities, as ascertained by VPC, were removed by chromatography on aluminium oxide (Merck Alumina, grade I), petroleum ether (b.p. 60-80°) being the eluent. The first group of fractions yielded the pure compound (b.p. 76° at 12 Torr), which was stored at -20°.

2-Chloro-4-methoxypyridine.

2-Chloropyridine 1-oxide hydrochloride was prepared by a slight modification of the method of Brown (32). It was found that the yield improves by keeping the solution of the chloro compound in the acetic-peracetic acid mixture at 40-45° overnight before heating at 70° for 3 hours. In subsequent steps, the hydrochloride was then converted into 2-chloro-4-nitropyridine 1-oxide (32), m.p. 155-156°, 2-chloro-4-nitropyridine (33), m.p. 52-53°, and 2-chloro-4-methoxypyridine (34), which was purified by fractional distillation, b.p. 106-107° at 16 Torr.

4-Chloro-2-methoxypyridine.

2-Chloro-4-aminopyridine was prepared by reduction (35) of 2-chloro-4-nitropyridine 1-oxide (see above) with iron and acetic acid in the presence of a little mercuric chloride, m.p. 90-91.5°. In subsequent steps, it was converted into the 2-methoxy-4-amino derivative, m.p. 88-89.5° (crude), lit. (36) m.p. 91.5-92°, and then into 4-chloro-2-methoxypyridine by the method described by Kolder and den Hertog (37) for related compounds. The final product was purified by fractional distillation, b.p. 71-71.5° (17 Torr) and m.p. 27-27.8°, lit. (38) m.p. 26°.

2,4-Dimethoxypyridine.

2,4-Dichloropyridine (2.98 g., 0.02 mole) was added to a sodium methoxide solution (prepared by dissolving 1.20 g. of sodium in 120 ml. of anhydrous methyl alcohol) in a heavy-walled tube. The tube was sealed and kept at 125° overnight. On cooling, a gas (dimethyl ether) was evolved from the reaction mixture. The contents of the tube were evaporated to dryness. Steam distillation of the residue yielded 1.94 g. of 2,4-dimethoxypyridine (67%), which was distilled at reduced pressure, b.p. 89-90° (12 Torr); picrate, m.p. 159-160°, lit. (39) m.p. 159°. The residue from the distillation was neutralized with 2*N* sulphuric acid and brought to dryness at reduced pressure. The residue was extracted for 48 hours in a Soxhlet apparatus with diethyl ether. From these extracts 0.31 g. of an oily product, which crystallized on prolonged standing, was obtained. This product was chromatographated on an alumina column, a 3% solution of methanol in benzene being the eluent. Among other products, which were not further investigated, substantial amounts of 2-methoxy-4-pyridone (m.p. 133-135°) and only a minor quantity of 4-methoxy-2-pyridone (m.p. 164-166°) were isolated. Mixed melting points with authentic specimens (40) showed no depression.

Product Analyses.

(a) Methoxydechlorination of 2,4-dichloropyridine. The reaction mixtures obtained from experiments carried out at 70.1, 80.3, 89.4, and 99.5° with equimolecular concentrations of the reactants were analysed by the VPC method employing a Perkin-Elmer model 800 fractometer operated with a Perkin-Elmer Golay "R" column at 175°, nitrogen being the carrier gas. The experimental technique was the one previously described (41). The results are as follows. 2-Methoxy-4-chloro and 4-methoxy-2-chloropyridine: 7.5 and 92.5% (at 70.1°); 8.2 and 91.8% (at 80.3°); 8.6 and 91.4% (at 89.4°); 9.2 and 90.8% (at 99.5°), respectively.

(b) Reaction of 2-chloro-4-methoxypyridine with methoxide ions. A solution of 2-chloro-4-methoxypyridine (0.5 g., 3.5 mmole) in 50 ml. of methanolic sodium methoxide (0.15 *M*) was divided into 2-ml. portions which were sealed in Pyrex tubes and then immersed in a constant temperature bath. Experiments with sets of six tubes each were carried out at 120, 130, 140, and 150°. The tubes were then removed at convenient time intervals and the content analysed by thin-layer chromatography on Merck F_{234} silica plates, a mixture of ethyl acetate, benzene and propyl alcohol being the eluent (ratio 29:7:4). On the same plate solutions

of the starting material, of 2,4-dimethoxypyridine, 2-methoxy-4-pyridone, and 4-methoxy-2-pyridone were always applied for comparison. In addition to the spots corresponding to initial substrate and expected substitution product, a third spot appeared as the reaction had progressed for about 30%. The latter spot proved to correspond to 2-methoxy-4-pyridone. In another experiment starting with 2,4-dimethoxypyridine a spot with R_f identical to that of the 2-methoxy-4-pyridone was distinctly detected on the thin-layer chromatogramme.

Kinetic experiments.

Anhydrous methanol and sodium methoxide solutions were prepared as described in a previous paper (25). The purity of the samples of the chloropyridines and chloropyrimidines was checked either by VPC or TLC.

Runs up to 45° were carried out in a volumetric flask, whereas all experiments at higher temperature were performed by using the sealed tube technique. The concentrations were in the range 0.01-0.05 *M* for the heterocyclic substrate and 0.02-0.11 *M* for the sodium methoxide reagent. The reaction rates were determined by analysing for the displaced chloride ion. Samples were quenched in 0.3 *M* nitric acid and titrated by the potentiometric method with a Radiometer (Copenhagen) model 22 *p*H-meter equipped with a P 401 silver electrode and a K 601 mercurous sulphate-potassium sulphate saturated reference electrode. Blank experiments showed that neither the chloro compounds nor the reaction products interfered with the potentiometric determination of the chloride ion.

Rate constants were obtained on plotting log (a-x)/(b-x) *vs* time and then corrected for the thermal expansion of methanol (42). In the case of 2-chloro-4-methoxypyridine, where the kinetics were complicated by the demethylation reaction of the product (see above), the second-order kinetic plots showed downward curvatures after 30-40% reaction and the rate constants were evaluated from the linear part of the plot. The over-all rate constants for the methoxy dechlorination of 2,4-dichloropyridine, 75.4 x 10^{-5} (at 70.1°), 18.9 x 10^{-4} (at 80.3°), 40.2 x 10^{-4} (at 89.4°), 91.2 x 10^{-4} (at 99.5°), and the isomer distribution reported above allowed to calculate (41) the partial rate constants for the substitution at the α-position as reported in the Table and below.

A total of 31 independent kinetic runs were carried out, and the results were as follows (k_2 x 10^5 $l \cdot mole^{-1} sec^{-1}$):

4,6-Dichloropyrimidine: 79.0 (at -30.0°), 257 (at -20.0°), 752.5 (at -10.0°), 2130 (at 0.0°).

4-Chloro-6-methylpyrimidine: 25.9 (at -5.0°), 74.5 (at 5.0°), 191 (at 15.0°), 482 (at 25.0°).

4-Chloro-6-methoxypyrimidine: 8.66 (at 15°), 26.7 (at 25.5°), 67.3 (at 35.0°), 168 (at 45.0°).

2,4-Dichloropyridine: 5.67 (at 70.1°), 15.4 (at 80.3°), 34.7 (at 89.4°), 83.7 (at 99.5°).

2-Chloropyridine: 12.2 (at 120.4°), 30.0 (at 130.3°), 75.8 (at 140.3°), 173 (at 150.3°).

2-Chloro-4-methoxypyridine: 8.38 (at 120.0°), 19.5 (at 130.0°), 47.3 (at 140°), 112 (at 150.0°).

The activation energies, E_{act}, and the frequency factors, $\log_{10}$ A, were calculated by the least square method from the Arrhenius equation; activation entropies, ΔS^*, and activation enthalpies, ΔH^*, from the usual equations (43,44).

The values for ΔS^* and ΔH^* reported in the Table are averages from those obtained by these equations at all the temperatures used for each substrate. The values of *k* are accurate to ± 2% or better, energies of activation to ± 0.4 kcal/mole, values of $\log_{10}$ A to ± 0.3 unit.

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Received August 5, 1969

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