however, that carbon shift data can be used to characterize the important resonance feature and thereby aid in the separation of these various effects in reaction rate or related equilibrium data. Thus, instead of the σ's for shifts and other chemical properties being totally unrelated, the information from the two sources is complementary and can be combined to characterize the relative importance of the component parts which affect the various σ's to differing degrees.

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Aromatic Substitution. XXVI.[1] Kinetics of Nucleophilic Substitution of Some Bromopyridines and -picolines with Methoxide, Thiomethoxide, Phenoxide, and Thiophenoxide Ions

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The rates and activation of parameters were determined for the reactions of KSMe in methanol with 2-bromo-, 2-bromo-3-methyl-, 2-bromo-5-methyl-, 2,3-dibromo-, and 2,5-dibromopyridine, and of KOMe, KOPh, KSMe, and KSPh with 2-bromo-, 2-bromo-3-methyl-, and 2-bromo-5-methylpyridine in hexamethylphosphoramide. The results confirm the previous conclusion that a 3-methyl substituent activates the 2 position in the case of attack by thiophenoxide ion (but not with the other three nucleophiles) because of a combination of ion–dipole and dispersion attractive forces between the 3 substituent and the PhS^-, and not because of a heavy (sulfur) nucleophile effect.

Quantitative studies[2] of the nucleophilic aromatic substitution of a hydride ion equivalent in the pyridine series by phenyllithium have established that a 3-methyl or a 3-ethyl group *activates* the 2 position of the pyridine nucleus toward this nucleophilic attack, methyl activating it more than ethyl. On the other hand, the 6 position was *deactivated* normally, as expected on the basis of the electron-donating effect of the alkyl group. In the reactions of 3-picoline with methyllithium[3] and with sodamide (Tschitschibabin reaction),[4] however, the 3-methyl substituent did not activate C-2, although attack still occurred predominantly at the 2 rather than at the 6 position. An ion–dipole attractive interaction between the 3-methyl group and the approaching methyllithium[3] or amide anion could account for these observations.[5] Steric acceleration of substitution at C-2 by the 3 substituent was considered but had to be rejected on the basis that a 3-methyl group was found to activate C-2 more than did a 3-ethyl group.[2] The normal deactivation of C-6, but the much lesser deactivation, or even net activation, of C-2 is not explained, contrary to what is stated,[6] by simple Hückel calculations of localization energies which do not take into account ortho effects by the substituent at C-3. Two possibilities were discussed to account for the results obtained in the phenyllithium reactions. (a) London dispersion forces[7] acting between the 3-alkyl substituent and the polarizable attacking nucleophile could lower the activation energy for attack at C-2 but not at C-6. (b) The formation of an electron-deficient type bond[8] between the 3-alkyl group and the organolithium compound would facilitate attack at C-2.

In order to decide between these alternatives, kinetic studies on two model systems were carried out. The reaction of 2-bromo-, 2-bromo-3-methyl-, and 2-bromo-5-methylpyridine with methoxide ion was studied under a variety of conditions.[9] The rates were in the order 2-bromo- > 2-bromo-3-methyl- > 2-bromo-5-methylpyridine and were dependent upon E_a. This order of reactivity parallels that found in the methyllithium and Tschitschibabin reactions but not in the phenyllithium reaction. The lesser deactivation of the ortho than the para position by a 3-methyl group was attributed[9] to an ion–dipole attraction[10] between the methoxide ion approaching the 2 position and the methyl group which more than compensates for the greater inductive effect of the substituent at the ortho than at the para position, and any steric hindrance by the 3 substituent[11] to approach.

In order to find a system that would provide a model for the relative reactivities observed with phenyllithium, the kinetics of the reaction of 2-bromopyridines (**1**) with phenoxide ion in methanol to give **2** were studied, in the hope that the highly polarizable thiophenoxide would lead to the London attractive forces[7] discussed above. Indeed, the sought-for order of reactivities was observed: 2-bromo-3-methyl- > 2-bromo- > 2-bromo-5-methylpyridine.[12] The

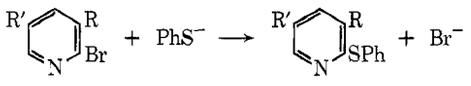
Table I
Kinetic Data for the Reaction of 2-Bromopyridines Derivatives with Potassium Thiomethoxide in Methanol

Pyridine	Registry no.	$10^4 k_2$, l. mol^{-1} sec^{-1} (temp, °C)					
2-Bromo-	109-04-6	2.29 (102.2)	3.74 (108)	6.65 (115)	10.0 (120)	14.5 (125)	22.2 (130)
2-Bromo-3-methyl-	3430-17-9	1.16 (100)	2.21 (108)	3.94 (115)	5.88 (120)	8.91 (125)	12.8 (130)
2-Bromo-5-methyl-	3510-66-5	0.274 (100)	0.594 (108)	1.07 (115)	1.70 (120)	2.53 (125)	3.85 (130)
2,3-Dibromo-	13534-89-9	7.52 (70)	18.6 (80.6)	40.9 (90.7)	83.6 (100.1)		
2,5-Dibromo-	624-28-2	3.11 (70)	7.54 (80)	16.9 (90)	24.9 (94.8)	39.4 (100.6)	

Table II
Activation Parameters for the Reaction of 2-Bromopyridine Derivatives with Potassium Thiomethoxide in Methanol[a]

Pyridine	$10^4 k_2$, l. mol^{-1} sec^{-1} (at 100°)	E_a,[b] kcal/mol	ΔS^*, eu	ΔF^*, kcal mol^{-1} (at 100°)
2-Bromo-	4.43 [0.944]	24.3 [26.8]	−12.9 [−9.2]	28.3
2-Bromo-3-methyl-	2.69 [0.24]	24.1 [27.8]	−14.5 [−9.5]	28.7
2-Bromo-5-methyl-	0.70 [0.15]	26.2 [29.0]	−11.6 [−7.4]	29.8
2,3-Dibromo-	168 [15.5]	20.3 [23.6]	−15.9 [−12.3]	25.5
2,5-Dibromo-	76.7 [15.2]	21.1 [24.7]	−15.5 [−9.4]	26.1

[a] Values in brackets are the corresponding values for MeO^-.[9] These have been recalculated using the same computer program as was used here for the thiomethoxide data. [b] Experimental errors are ±0.2 kcal in E_a and ±0.4 eu in ΔS^*.



1 2

ortho effect arose from a decrease in the energy of activation (ΔE_a = 2 kcal/mol). To decide between the dispersion forces and ion–dipole attractive interaction possibilities the kinetics of the reaction of 2,3- and 2,5-dibromopyridine with thiophenoxide ion in methanol were studied.[12] It was expected if only London dispersion forces were at work that a larger ortho:para ratio would be observed with the more polarizable β-bromo substituent than with methyl. If only ion–dipole interactions[10,13] were involved then $k_{o\text{-Br}}$ would be predicted to be smaller than $k_{p\text{-Br}}$ since the polarity of the $\overrightarrow{C\text{–}Br}$ bond is the reverse of that of the $\overleftarrow{C\text{–}CH_3}$ bond. In fact, the ortho:para ratio was not smaller than unity *nor* was it larger than that for a β-methyl substituent, and it was concluded that a combination of *both* polarizability effects *and* ion–dipole interactions had to be taken into account to explain the observed results.

In order to determine if the activation of C-2 by a 3-methyl group toward attack by thiophenoxide ion is due to a specific sulfur (heavy) nucleophile effect[14] or if the overall polarizability of the nucleophile[12,15] determined the magnitude of the attractive interactions with an ortho substituent, attention was turned to the reactions of 2-bromopyridine derivatives (1) with potassium thiomethoxide and with potassium phenoxide in methanol. The results of the kinetics of the reaction of 1 with KSMe are summarized in Tables I and II.

The data show that a 3-Me group does not activate C-2 toward attack by MeS^- in methanol. Indeed, the behavior observed is similar to that of methoxide ion in methanol and to the Tschitschibabin and methyllithium reactions, with the order of reactivities 2-bromo- > 2-bromo-3-methyl- > 2-bromo-5-methylpyridine. In this case, E_a values for 2-bromo- and 2-bromo-3-methylpyridine are essentially the same (as opposed to the case with MeO^-) and the slightly lower rate of reaction of 2-bromo-3-methylpyridine is due to a somewhat lower entropy of activation. The absence of activation of C-2 toward attack by MeS^- indicates that more than just a sulfur nucleophile effect is important in causing activation. It seems reasonable to suggest that the overall polarizability of the nucleophile plays the dominant role in determining whether or not a β-methyl group activates C-2; *e.g.*, phenyllithium is more polarizable than methyllithium.

Table III
Calculated Rate Ratios for the Reactions of 3-R- or 5-R-2-Bromopyridines with Potassium Methoxide and Potassium Thiomethoxide in Methanol at 110°

R	$k_{o\text{-R}}:k_{p\text{-R}}$	$k_{(MeS^-:k_{MeO^-})R}/(k_{MeS^-}:k_{MeO^-})_H$	$(k_{MeS^-}:k_{MeO^-})_{o\text{-R}}/(k_{MeS^-}:k_{MeO^-})_{p\text{-R}}$
CH_3	3.9 (MeS^-) 1.6 (MeO^-)	2.4 (*o*-Me), 0.96 (*p*-Me)	2.4
Br	2.2 (MeS^-) 1.0 (MeO^-)	2.3 (*o*-Br), 1.1 (*p*-Br)	2.2

The greater reactivity of 2-bromo-3-methyl- than of 2-bromo-5-methylpyridine with thiomethoxide ion is due to a lower energy of activation with the former (ΔE_a = 2.1 kcal/mol). This lesser deactivation of C-2 than C-6 could again be due either to London dispersion forces or to ion–dipole attraction, and to try to distinguish between these two possibilities the reactions of 2,3- and 2,5-dibromopyridine with MeS^- in methanol were studied, the rationale being as above for MeO^-. The ortho:para ratios were calculated directly as well as by the methods of Reinheimer and Bunnett[7] and of Sisti and Lowell,[16] the latter two approaches being used to cancel out nucleophilicity differences between the reagents MeS^- and MeO^-. These ratios are given in Table III.

Regardless of which rate ratios are considered, the data are not consistent with the involvement of either purely ion–dipole interactions, since the ortho:para ratio for a β-bromo substituent is not <1, or of purely polarizability effects, since the *o*-Br:*p*-Br ratio is not greater than the *o*-Me:*p*-Me ratio. A combination of these two factors[12] would

Table IV
Rate Ratios for the Reacton of 2-Bromo, 2,3-Dibromo-, and 2,5-Dibromopyridine with Methoxide, Thiomethoxide, and Thiophenoxide Ions at 110°

Nucleophile	2,3-Br_2:2-Br	2,5-Br_2:2-Br
$^-OCH_3$	16	16
$^-SCH_3$	38	17
^-SPh	50	20

Table V
Differences in Arrhenius Parameters

	Substituent in 2-bromopyridine				
	H	3-Me	5-Me	3-Br	5-Br
$\Delta E_a(E_{MeO^-} - E_{MeS^-})$	2.5	3.7	2.8	3.3	3.6
$\Delta\Delta S^*(MeO^- - MeS^-)$	3.7	5.0	4.2	3.6	6.1
$\Delta E_a(E_{MeO^-} - E_{PhS^-})$	1.2	3.0	2.6	2.4	1.3
$\Delta\Delta S^*(MeO^- - PhS^-)$	6.4	7.2	8.7	6.9	5.9

Table VI
Kinetic Data for the Reaction of 2-Bromopyridines with Methoxide, Thiomethoxide, Phenoxide, and Thiophenoxide Ions in HMPA

Pyridine	Nucleophile	$10^3 k_2$, l. mol^{-1} sec^{-1} (temp, °C)	$10^3 k_2$ (110°) calcd
2-Br	CH_3O^-	1.98 (30), 7.7 (48), 16.1 (58)	339
2-Br-3-CH_3	CH_3O^-	1.08 (30), 4.53 (48), 9.18 (58)	219
2-Br-5-CH_3	CH_3O^-	0.53 (30), 2.32 (48), 5.0 (58)	135
2-Br	PhO^-	0.72 (88.7), 3.4 (110.8), 6.83 (120.9)	3.13
2-Br-3-CH_3	PhO^-	0.42 (90), 2.26 (110.8), 4.33 (120.6)	2.1
2-Br-5-CH_3	PhO^-	0.094 (90), 0.457 (110.8), 1.0 (120.4)	0.42
2-Br	CH_3S^-	12.66 (28), 32.6 (42), 82.2 (55)	1740
2-Br-3-CH_3	CH_3S^-	5.76 (28), 15.7 (42), 38.8 (55)	742
2-Br-5-CH_3	CH_3S^-	1.33 (30), 4.16 (42), 14.1 (55)	389
2-Br	PhS^-	2.34 (80), 9.96 (100.2), 20.4 (110.2)	20.2
2-Br-3-CH_3	PhS^-	3.4 (80), 12.8 (100.2), 28.6 (110.2)	28.3
2-Br-5-CH_3	PhS^-	0.77 (90), 3.82 (110), 7.94 (120)	3.8

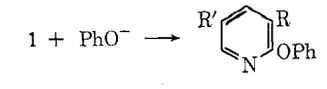
best account for the results. A comparison of the rate ratios given in Table IV shows that as the polarizability of the nucleophile increases from MeO^- through MeS^- to PhS^- the activating influence of a 3-bromo substituent increases, while a 5-bromo substituent exerts an activating ($-I > +M$) effect independent of the polarizability of the attacking nucleophile.

Another way of looking at this "ortho effect" which does take into account the differences in nucleophilicities between the reagents is to consider the differences in Arrhenius parameters of these reactions as a function of the nature and position of the substituent. These data are given in Table V along with the corresponding data for thiophenoxide ion.[16] For a 3-methyl substituent the ΔE_a value is larger than that for a 5-methyl substituent ($\Delta\Delta E_a = 0.9$ for MeO^- compared with MeS^-, $\Delta\Delta E_a = 0.4$ for MeO^- compared with PhS^-). If the polarizability of the sulfur atom were not taken into account, an unfavorable steric effect with the sulfur nucleophile should have resulted in a trend in ΔE_a in the opposite direction. When MeO^- and PhS^- are compared, ΔE_a for 3-Br is larger than ΔE_a for 5-Br ($\Delta\Delta E_a = 1.3$), and this difference is larger than that (0.4) for the β-methyl groups. This suggests that for PhS^- the polarizability factor is more important than the Coulombic interaction. On the other hand, when MeO^- is compared with MeS^-, ΔE_a for 3-Br (3.3) is not as large as ΔE_a for 5-Br (3.6), which suggests that polarizability is not as important with thiomethoxide as it is with thiophenoxide.

To complete the comparison between thiophenoxide as a nucleophile and the oxygen analogs it was necessary to study the kinetics of the reaction of phenoxide ion with bromopyridines. Preliminary runs of the reaction of potassium phenoxide with 2-bromopyridine in methanol were carried out with equivalent amounts of potassium methoxide and phenol in methanol. With 2-bromopyridine at 100° for 102 hr it gave an almost quantitative yield of 2-methoxypyridine (ratio of 2-methoxy-:2-phenoxypyridine 49:1 by gas chromatography), which is not unexpected, for though the equilibrium $MeOH + PhO^- \rightleftharpoons MeO^- + PhOH$ lies largely to the left, methoxide is a much stronger nucleophile than is phenoxide. In many of the studies involving phenoxide ion in alcoholic solvents an excess of free phenol was employed to control the alkoxide ion concentration.[17-20] In the present study, 18 equiv of PhOH was required to suppress almost completely competition from MeO^- (2-methoxy-:2-phenoxypyridine 1:99). The usefulness of having an excess of free phenol vanished, however, when it was found that 2-bromopyridine reacted with phenol in the absence of base at 120° for 120 hr to give 2-phenoxypyridine in 76% yield, probably *via* the bromopyridinium ion.

In order to bypass the difficulties encountered with phenoxide ion in a protic solvent attention was turned to the use of a dipolar aprotic solvent in which competition from the solvent would be eliminated. Hexamethylphosphoramide (HMPA) was selected as the medium for kinetic studies with phenoxide ion, since it is stable to nucleophiles[21] and is not hydrolyzed in alkaline media. In addition, it is of interest that no nucleophilic substitutions have so far been reported as far as we know for pyridine derivatives in HMPA.

To determine the potential usefulness of such studies preliminary measurements were made of the relative reactivities in HMPA using the competitive technique in which equimolar mixtures of 2-bromo- and 2-bromo-3-methyl-, or 2-bromo- and 2-bromo-5-methylpyridine were allowed to react with a small amount of potassium phenoxide. The reaction products were analyzed by gas chromatography and the total rate ratios were calculated. Authentic samples of the 2-phenoxypyridines were prepared for comparison



with the reaction products. The order of reactivities was found to be 2-bromo- > 2-bromo-3-methyl- > 2-bromo-5-methylpyridine; $^{o\text{-Me}}K_H = 0.47$ and $^{p\text{-Me}}K_H = 0.099$; ortho:para ratio (at 80° in HMPA) 4.8. This order of reactivity parallels those found in the Tschitschibabin and methyllithium reactions.

In order to compare the reactivity of PhO^- with those of MeO^-, MeS^-, and PhS^- it was necessary to carry out kinetic measurements of the reactions of the bromopyridines with these nucleophiles in HMPA. The specific rate constants so obtained are summarized in Table VI. These reveal that a 3-methyl group does not activate C-2 in 2-bro-

Table VII
Comparison of Rate Constants for Reactions of Bromopyridines in MeOH, HMPA, and DMSO at a Common Temperature

Pyridine	Nucleophile	$10^3 k_2$ (110°) in HMPA	$10^3 k_2$ (110°) in MeOH	$10^3 k_2$ (110°) in DMSO (1% MeOH)
2-Br	CH_3O^-	339	0.0944[a]	309[b]
2-Br-3-CH_3	CH_3O^-	219	0.0239[a]	170[b]
2-Br-5-CH_3	CH_3O^-	135	0.0154[a]	117[b]
2-Br	PhS^-	20.2	0.0214[a]	2.3[b]
2-Br-3-CH_3	PhS^-	28.3	0.0300[a]	
2-Br-5-CH_3	PhS^-	3.8	0.0061[a]	
2-Br	CH_3S^-	1740	0.443	
2-Br-3-CH_3	CH_3S^-	742	0.269	
2-Br-5-CH_3	CH_3S^-	389	0.097	

[a] See ref 12. [b] See ref 9.

Table VIII
Arrhenius Parameters for the Reactions of 2-Bromopyridine Derivatives with OCH_3^-, PhO^-, CH_3S^-, and PhS^- Ions in HMPA and MeOH

Pyridine	Nucleophile	E_a (HMPA)[a]	E_a (MeOH)	ΔS^*(HMPA)	ΔS^*(MeOH)
2-Br	CH_3O^-	14.8 [17.9][d]	26.8[b]	−24.0 [−18.1][d]	−9.2
2-Br-3-CH_3		15.2 [18.7]	27.8[b]	−23.9 [−16.9]	−9.5
2-Br-5-CH_3		16.0 [19.5]	29.0[b]	−22.8 [−16.2]	−7.4
2-Br	PhO^-	19.8		−20.7	
2-Br-3-CH_3		21.9		−16.3	
2-Br-5-CH_3		21.8		−19.3	
2-Br	PhS^-	19.2 [22.3][d]	25.6[b]	−18.5 [−13.0][d]	−15.6[b]
2-Br-3-CH_3		17.4	24.8[b]	−22.8	−16.7[b]
2-Br-5-CH_3		22.1	26.4[b]	−14.3	−16.1[b]
2-Br	CH_3S^-	13.6	24.3[c]	−24.1	−12.9[c]
2-Br-3-CH_3		13.7	24.1[c]	−25.2	−14.5[c]
2-Br-5-CH_3		18.1	26.2[c]	−14.0	−11.6[c]

[a] Experimental errors are ±0.4 kcal in E_a and ±0.8 eu in ΔS^*. [b] See ref 9, 12, and 16. Experimental errors are ±0.3 kcal in E_a and ±1 eu in ΔS^*. [c] See Table II. Experimental errors are ±0.2 kcal in E_a and ±0.4 eu in ΔS^*. [d] Values in brackets are corresponding values in DMSO; see ref 9 and 12.

mopyridine toward attack by the MeO^-, PhO^-, and MeS^- ions, but does in the case of PhS^- anion in HMPA. This is similar to the behavior in methanol. Thus, phenoxide is not polarizable enough to lead to overall activation so that, in that sense, the sulfur atom is essential. These results are in keeping with the suggestion that the overall polarizability of the nucleophile plays the dominant role in determining whether or not a β-methyl group activates C-2. In all cases except for PhS^- the order of reactivities was 2-bromo- > 2-bromo-3-methyl- > 2-bromo-5-methylpyridine.

The reactions in HMPA were faster (by *ca.* 10^3) than those in methanol (Table VII), and slightly more so than those in DMSO (1% MeOH).[12] The Arrhenius parameters for the reactions in HMPA are summarized in Table VIII, in which the corresponding data for the reactions in methanol and DMSO are included for ease of comparison. The increased rates in HMPA are due to a reduction of 5–13 kcal/mol in E_a, somewhat counterbalanced by lower ΔS^* values ($\Delta\Delta S^* = \Delta S^*_{MeOH} - \Delta S^*_{HMPA}$ = 4–15 eu, except for the reaction of 2-bromo-5-methylpyridine with MeS^- and PhS^-). These ΔS^* values in HMPA reflect the expected[12,19] decrease in solvation of the anionic nucleophiles in the ground state, since HMPA is expected to solvate cations best.[21] HMPA forms a solvation shell around the smaller anions MeO^- and MeS^- less readily ($\Delta\Delta S^* = \Delta S^*_{MeOH} - \Delta S^*_{HMPA}$ = *ca.* 12 eu) than around the larger thiophenoxide ion ($\Delta\Delta S^*$ = *ca.* 5 eu). Again, a comparison of ΔS^* for MeO^- *vs.* PhO^-, as well as MeS^- *vs.* PhS^- (Table VIII), shows that the smaller nucleophiles give rise to the lower value of ΔS^*. In the case of the sulfur nucleophiles the order $\Delta S^*_{MeS^-} < \Delta S^*_{PhS^-}$ in HMPA is the reverse of the order in methanol, in which differences in ion solvation are less pronounced and the full effect of the steric interactions for the larger PhS^- emerge. Comparison of $^-OCH_3$ with another relatively small nucleophile, $^-SCH_3$, in HMPA shows little difference between the ΔS^* values; this similarity is what is predicted if solvation effects influence the magnitude of ΔS^* to a greater extent than heavy nucleophile steric interactions between entering and leaving groups. The choice of a solvent, methanol or HMPA, appears to have little effect, however, upon the relative magnitudes of ΔS^* within a group of three bromopyridines for each nucleophile. For methoxide ion in methanol these differences in entropies of activation, though small, have been accounted for[9] on the basis of differences in solvation of the ground states and the transition states. In the present cases, other factors need to be taken into account also, such as adverse steric interactions at a nonbonding level below that at which there are substantial increases in ΔH^* (*e.g.* steric effect by a 3-CH_3 group upon the rotational degrees of freedom of the bulky sulfur nucleophile in the transition state for attack at C-2),[22] steric interactions between the sulfur nucleophile and the departing bromine atom, and differences in the degrees of solvation of the transitions states in HMPA for the various substituted pyridines. This is discussed in detail elsewhere.[23]

Experimental Section

Materials. HMPA (Dow Chemical Co.) was fractionally distilled, the fraction of bp 65–66° (1 mm) being used. The purification of methanol, 2-bromo-, 2-bromo-3-methyl-, and 2-bromo-5-methylpyridine was as previously reported.[9] 2,5-Dibromopyridine was recrystallized from ethanol and had mp 94° (lit.[24] mp 94°). The preparation of 2,3-dibromopyridine was reported previously.[12]

Solutions of potassium thiomethoxide in methanol were prepared by dissolving solid potassium thiomethoxide in pure methanol and storing the solutions under nitrogen. These solutions were standardized by direct titration with hydrochloric acid. Potassium thiomethoxide was prepared[25] by adding an excess of methyl mercaptan to a methanolic solution of potassium methoxide (200 ml, 0.5 *M*). To this solution toluene (200 ml) was added, and the resulting mixture was distilled until the boiling point of toluene (110°) was reached. The potassium thiomethoxide precipitated as a fine crystalline mass and was dried at 100° (1 mm) for 12 hr.

Solutions of potassium phenoxide in methanol were prepared by adding an equivalent amount of potassium methoxide in methanol to a weighed amount of phenol.

Solutions of potassium methoxide, potassium thiomethoxide, potassium phenoxide, and potassium thiophenoxide in HMPA were prepared by dissolving the corresponding salt in pure HMPA.

The solutions were standardized by potentiometric titration with standard hydrochloric acid (0.00232 *M*). Potassium methoxide was prepared by the addition of pure potassium metal (4 g) in small portions to dry methanol (250 ml) under a nitrogen atmosphere. The methanol was removed on a film evaporator and the resulting white solid was dried at 60° (1 mm) for 12 hr. Potassium phenoxide was prepared from phenol by the procedure of Kornblum and Lurie.[26] Solid potassium thiophenoxide was prepared by the procedure previously reported.[12]

Reaction Products. These were obtained by a preparative reaction of the appropriate 2-bromopyridine with potassium thiomethoxide in methanol and with potassium methoxide, thiomethoxide, phenoxide, and thiophenoxide in HMPA under the conditions of the kinetic runs. 2-Methoxypyridine had bp 138–140° (755 mm) [lit.[9] bp 140–142° (740 mm)]. 2-Methoxy-3-methylpyridine had bp 157–159° (750 mm) [lit.[9] bp 38° (6 mm)]. 2-Methoxy-5-methylpyridine had bp 39–40° (2 mm) [lit.[9] bp 52° (6 mm)]. 2-Thiophenoxypyridine had bp 123–124° (1 mm) [lit.[27] bp 160–162° (8 mm)]. 3-Methyl-2-thiophenoxypyridine had bp 132–133° (1 mm) [lit.[12] bp 142–144° (2 mm)]. 5-Methyl-2-thiophenoxypyridine had bp 139–140° (1 mm) [lit.[12] bp 148–150° (2 mm)]. 2-Phenoxypyridine (from light petroleum) had mp 41–42° (lit.[28] mp 42–44°). 2-Thiomethoxypyridine had bp 54–55° (3 mm) [lit.[29] bp 197° (760 mm)].

3-Methyl-2-thiomethoxypyridine had bp 61–62° (2.6 mm) (61%). The picrate (from methanol) had mp 119–120°.

Anal. Calcd for $C_7H_9NS,C_6H_3N_3O_7$: C, 42.39; H, 3.26. Found: C, 42.49; H, 3.34.

Nmr (CCl_4) of free base: δ 8.17 (1 H, q, $J_{5,6}$ = 4.6, $J_{4,6}$ = 1.8 Hz, H-6), 7.14 (1 H, q, $J_{4,5}$ = 7.9 Hz, H-4), 6.74 (1 H, q, H-5), 2.48 (3 H, s, CH_3S), 2.19 (3 H, s, CH_3).

5-Methyl-2-thiomethoxypyridine had bp 70–71° (2.6 mm) (53%).

Anal. Calcd for C_7H_9NS: C, 60.39; H, 6.52. Found: C, 60.46; H, 6.75.

The picrate (from methanol) had mp 181–182°.

3-Bromo-2-thiomethoxypyridine had bp 71–72° (2 mm) (56%).

Anal. Calcd for C_6H_6BrNS: C, 35.31; H, 2.96. Found: C, 35.37; H, 2.98.

5-Bromo-2-thiomethoxypyridine (from ethanol) had mp 40–41° (83%), nmr (CCl_4) δ 8.43 (1 H, d, $J_{4,6}$ = 1.3 Hz, H-6), 7.48 (1 H, q, $J_{3,4}$ = 4.5 Hz, H-4), 7.00 (1 H, d, H-3), 2.50 (3 H, s, CH_3).

Anal. Calcd for C_6H_6BrNS: C, 35,31; H, 2.96. Found: C, 35.47; H, 2.99.

3-Methyl-2-phenoxypyridinehad bp 101–102° (1 mm) (81%), nmr (CCl_4) δ 7.80 (1 H, q, H-6), 7.12 (6 H, m, H-4 and C_6H_5), 2.67 (3 H, s, CH_3).

The picrate (from methanol) had mp 145–146°.

Anal. Calcd for $C_{12}H_{11}NO$, $C_6H_3N_3O_7$: C, 52.17; H, 3.38. Found: C, 52.12; H, 3.48.

5-Methyl-2-phenoxypyridinehad bp 81° (0.1 mm) (78%), nmr (CCl_4) δ 7.80 (1 H, d, H-6), 7.16 (6 H, m, H-4 and C_6H_5), 6.70 (1 H, d, $J_{4,5}$ = 4 Hz, H-5), 2.20 (3 H, s, CH_3).

Anal. Calcd for $C_{12}H_{11}NO$: c, 77.81; H, 5.99. Found: C, 77.83; H, 6.06.

Kinetic Procedures. A. Potassium Thiomethoxide in Methanol. The runs were carried out in sealed tubes under nitrogen using 5-ml portions of solutions containing equimolar (*ca.* 0.0095 *M*) proportions of potassium thiomethoxide and the 2-bromopyridine. Aliquots were quenched in ice. The time at which the first tube was removed from the oil bath was taken as zero time. The kinetics were followed by estimating unreacted thiomethoxide ion by potentiometric titration with dilute hydrochloric acid [time in minutes, titer for thiomethoxide determination *vs.* 0.0244 *M* HCl (*a* = 18.00 ml)]: 0, 17.71; 30, 15.80; 60, 14.43; 90, 13.06; 115, 12.21; 150, 11.13; 180, 10.43; $k_2 = 1.00 \times 10^{-3}$ l. mol^{-1} sec^{-1}.

B. Potassium Thiophenoxide in HMPA. Equimolar amounts of the 2-bromopyridine and potassium thiophenoxide in HMPA (*ca.* 4.0 mequiv in 3.95 ml) were sealed in glass tubes under nitrogen. Tubes were submerged in a thermostat and allowed 10 min to attain thermal equilibrium. Aliquots were quenched at regular intervals by addition to dilute hydrochloric acid (40 ml, 0.00757 *M*). The kinetics were followed by measuring unreacted thiophenoxide by back titration with barium hydroxide solution (0.0090 *M*).

C. Potassium Methoxide and Thiomethoxide in HMPA. Equimolar amounts of the 2-bromopyridine and potassium methoxide (or thiomethoxide) were combined in a flask under nitrogen. The flask was immersed in a thermostat and allowed 5 min for thermal equilibration. Aliquots (2.0 ml) were quenched in hydrochloric acid (30 ml, 0.00757 *N*) and the excess acid was back-titrated with barium hydroxide solution (*ca.* 0.005 *N*).

D. Potassium Phenoxide in HMPA. The runs were carried out in sealed tubes under nitrogen using 1.97-ml portions of a solution containing equimolar (0.0033 mol) proportions of the 2-bromopyridine and potassium phenoxide. Aliquots were quenched in halide-free nitric acid (*ca.* 30 ml, 0.1 *M*), and liberated bromide ion was titrated against silver nitrate (0.0010 *M*) potentiometrically using a calomel reference cell and a bromide-specific electrode (Orion).

Competitive Reactions of 2-Bromopyridine and 2-Bromomethylpyridines with Potassium Phenoxide in HMPA. 2-Bromopyridine (1.3144 g, 0.0083 mol), 2-bromo-3-methylpyridine (1.4311 g, 0.0083 mol), and potassium phenoxide (0.3689 g, 0.00279 mol) were dissolved in HMPA (12 g) in a dry Pyrex tube. The tube was sealed under nitrogen and suspended in a thermostat at 80°. After 142 hr biphenyl (0.1105 g) was added as internal standard and also water (75 ml). The aqueous layer was extracted with ether (5 × 75 ml), and the combined ethereal extracts were washed with water (2 × 75 ml), dried, concentrated to 10 ml, and analyzed by glc on a 6 ft × 0.25 in. column packed with SE-52 (10%) on Chromosorb W (60–100 mesh) at 160° and a 60 ml/min He flow rate. The total rate ratio was calculated using the Ingold–Shaw equation[30] and found to be $^{o\text{-Me}}K_H = 0.47 \pm 0.005$. When 2-bromo-5-methylpyridine was used $^{p\text{-Me}}K_H = 0.099 \pm 0.002$.

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Registry No.—Potassium methoxide, 865-33-8; potassium thiomethoxide, 26385-24-0; potassium phenoxide, 100-67-4; potassium thiophenoxide, 3111-52-2; 3-methyl-2-thiomethoxypyridine, 51933-73-4; 3-methyl-2-thiomethoxypyridine picrate, 51933-74-5; 5-methyl-2-thiomethoxypyridine, 51933-75-6; 5-methyl-2-thiomethoxypyridine picrate, 51933-76-7; 3-bromo-2-thiomethoxypyridine, 51933-77-8; 5-bromo-2-thiomethoxypyridine, 51933-78-9; 3-methyl-2-phenoxypyridine, 51933-79-0; 3-methyl-2-phenoxypyridinepicrate, 51933-80-3; 5-methyl-2-phenoxypyridine, 51933-81-4.

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Products and Mechanisms in the Anodic Oxidation of N,N-Dimethylbenzylamine in Methanol

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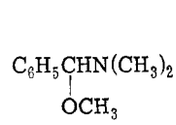
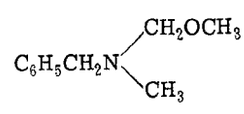
The anodic oxidation of N,N-dimethylbenzylamine has been studied in methanol–tetra-n-butylammonium fluoroborate and in methanol–potassium hydroxide. The major oxidation mechanism is of the ECE type and initiated by electron transfer from the amine substrate. The initially formed cation radical loses a proton and transfers an electron in subsequent steps to give cations, which react with available nucleophiles to yield the final products. The relative amount of attack on the methyl and benzyl positions is determined by the nature of the base participating in the proton transfer. When the base is the amine substrate, attack on methyl is strongly favored. When a strong base, *e.g.*, hydroxide ion or methoxide ion, is involved, the direction of attack is very nearly in accord with statistical expectations.

The anodic methoxylation of N,N-dimethylbenzylamine in methanol–potassium hydroxide affords two substitution products, α-methoxy-N,N-dimethylbenzylamine (I) and N-methoxymethyl-N-methylbenzylamine (II), in the ratio



I



II

of 1:4.[1] Weinberg and Brown[1] proposed that this oxidation was initiated by electron transfer from the amine, but Smith and Mann[2] suggested that the oxidation resulted from the attack on the substrate of anodically generated methoxyl radicals. In later work[3] Weinberg supported his proposal by demonstrating that significant methoxylation occurs only at potentials greater than the half-wave potential for N,N-dimethylbenzylamine oxidation (0.92 V *vs.* sce at a rotating platinum microelectrode in acetonitrile containing 0.5 *M* lithium perchlorate).

The preference for substitution of the methyl group was contrary to *a priori* expectation and was even more pronounced in the anodic cyanation of N,N-dimethylbenzylamine, where substitution occurred exclusively on the methyl group.[4] Both Weinberg[3] and Andreades[4] have invoked adsorbed intermediates, in which the methyl group of the adsorbed species is more accessible to chemical attack, to account for the observed direction of substitution.

However, many homogeneous, chemical oxidations of N,N-dimethylbenzylamine, all initiated by an electron transfer from the amine to form an aminium cation radical, show preferential attack on the methyl group. Some examples are the oxidation by chlorine dioxide in aqueous solution,[5] the oxidation by potassium hexacyanoferrate(III) in 2 *M* potassium hydroxide,[6] and the photochemical oxidation by 4-benzoylbenzoic acid in 2:1 *tert*-butyl alcohol–water.[7] It is, therefore, possible that the observed preferential attack on the methyl group is a, as yet incompletely understood, characteristic reaction of the amine cation radical and does not involve the intervention of the electrode surface. To explore this possibility we have carried out a more detailed study of the anodic oxidation of N,N-dimethylbenzylamine.

Cyclic Voltammetry. Fleischmann and Pletcher[8] have reported that the solvent decomposition potential, defined as the potential above which the current is greater than 10 mA/cm², for the acetonitrile–0.14 *M* tetraethylammonium fluoroborate electrolyte exceeds 3 V *vs.* Ag/Ag$^+$ 10^{-2} *M*. On cyclic voltammetry of dimethylbenzylamine in acetonitrile–0.1 *M* tetra-n-butylammonium fluoroborate, the peak current varied linearly with the amine concentrations, and the peak potential occurred at 0.86 V *vs.* sce, a value in reasonable agreement with the polarographic half-wave potential reported by Weinberg.[3]

Figure 1 shows a cyclic voltammogram for 0.6 *M* dimethylbenzylamine in methanol–0.5 *M* potassium hydroxide at a scan speed of 200 mV/sec. The concentrations are those used in the preparative experiments to be described later. Curve A is for the electrolyte alone and curve B is with added amine. Below 1.1 V *vs.* sce the observed currents are actually depressed by the addition of the amine, and this is in qualitative agreement with a similar observation, based on Tafel plots, made by Weinberg.[3] Above 1.1 V the currents are higher with the amine present. Both dimethylbenzylamine and methoxide ion are being oxidized simultaneously, and the waves for the two oxidations are not fully separable.

The solvent decomposition potential for methanol–0.4 *M* tetra-n-butylammonium fluoroborate is approximately 1.3 V *vs.* sce. In this electrolyte methoxide ion is absent, and the current increase above 1.3 V is due to oxidation of methanol. The cyclic voltammogram at a scan speed of 200 mV/sec for 0.6 *M* dimethylbenzylamine in this electrolyte is shown in Figure 2. The concentrations used are again those of preparative experiments. In this system the wave for the amine oxidation is clearly separable from the background, and the peak potential is 0.94 V *vs.* sce.

More detailed cyclic voltammetry studies in both acetonitrile and methanol, with 2.96×10^{-2} amine and 0.1 *M* tetra-n-butylammonium fluoroborate, satisfy the theoretical criteria, developed by Nicholson and Shain,[9] for an