fibrous solid was filtered, washed thoroughly with hexane, and dried. It was then cut into small pieces and shredded in a blender under hexane. Filtration and subsequent drying at 100° (1 mm) gave 46.8 g (94.7%) of snow-white polymer: DTA, small endotherms at 80° and 117°, degradation endotherm peaks at 450°; TGA, 5% weight loss at 381°, 94.7% loss at 500°; inherent viscosity (0.1% in $CHCl_3$) 1.62.

Anal. Calcd for $(C_5H_6N_2)_n$: C, 63.8; H, 6.43; N, 29.8. Found: C, 63.5; H, 6.47; N, 29.7; mol wt (osmometric in dioxane), 148,500.

In similar experiments polymers with inherent viscosities of 3.13 and 1.76 and apparent mol wt of 250,000–360,000 were obtained.

Poly(2-propenylpyrazole).—To a solution of 50 ml of 1-(2-propenyl)pyrazole in 100 ml of benzene was added about 4 mg of azobisisobutyronitrile and the solution was stirred at 80° for 30 min. Another 4 mg of initiator was added and this was repeated after another 20 min. After a total of 3 hr at 80°, the thick solution was poured into 2 l. of stirred hexane. A solid which precipitated was filtered, washed with hexane, and dried *in vacuo*. The polymer was obtained in 32-g (67%) yield.

Anal. Calcd for $(C_6H_8N_2)_n$: C, 66.6; H, 7.46; N, 25.9. Found: C, 65.7; H, 7.44; N, 26.2.

Registry No.—**1**, 20173-98-2; **2**, 25834-28-0; **3**, 25834-29-1; **4**, 25834-30-4; **5**, 25834-31-5; **6**, 25834-32-6; **7**, 25834-33-7; **8**, 25834-34-8; **9**, 25834-35-9; **10**, 25834-36-0; **11**, 25834-37-1; **12**, 25834-38-2; 1-vinylpyrazole polymer, 25823-41-0; poly(2-propenylpyrazole), 25823-42-1.

Cleavage of Pyridyl Methyl Ethers and Reactions of 3-Halopyridines with Sodium Methoxide

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2-, 3- and 4-methoxypyridine and also anisole are readily cleaved to their hydroxy arenes and methyl ether in an SN2 reaction by sodium methoxide in methanol. At 164.7° the methoxypyridines react at relative rates 1.0:1.1:2.8, respectively. Using CD_3OD–D_2O as solvent and nmr analysis, it was possible to distinguish between CH_3OCD_3 and CH_3OD reaction products and thereby show that deuterioxide ion does not compete with methoxide ion in the cleavage of 3-methoxypyridine. With 4-methoxypyridine, methoxyl group exchange is faster than the formation of 4-hydroxypyridine. 3-Methoxypyridine undergoes hydrogen–deuterium exchange in the order H-4 > H-5 > H-2; no exchange at H-6 was observed. Hydrogen–deuterium exchange took place at H-3,5 but not at H-2,6 of 4-methoxypyridine. At 218°, 3-chloro- and 3-bromopyridine react with sodium methoxide to give 3-methoxypyridine which then undergoes ether cleavage. The concentrations of all pyridines in the consecutive reactions were followed by nmr. The ratios of the second-order rate constants for methoxy dehalogenation and ether cleavage at 218° are 0.53 and 0.75, respectively. Reactions leading to hydroxy compounds are of preparative value. No evidence was found for the formation of 3,4-pyridyne by dehydro halogenation of the halopyridines.

The preferred general method of cleaving ethers continues to involve the use of a strong acid.[1,2] Cleavage of ethers by bases, however, is regarded more as a curiosity, if not as an undesirable side reaction.[3] It has been suggested that cleavage of ethers by alcoholic KOH is of no preparative value.[4]

We wish to report the results of some preparative and kinetic studies of the methoxide ion induced cleavage of pyridyl methyl ethers. These studies were designed to (1) show that the cleavage reaction is of preparative value, (2) provide evidence for the expected SN2 mechanism, (3) obtain a measure of the ability of the aryl group to influence reactivity, (4) determine whether in a methanol–water mixture hydroxide ion competes with methoxide ion, and (5) determine the ability of a polar, aprotic solvent to influence the rate of ether cleavage.

We also report that 3-chloro- and 3-bromopyridine undergo methoxy dehalogenation at rates slightly slower than the accompanying ether cleavage.

Results and Discussion

Ether Cleavage.—3-Methoxypyridine undergoes cleavage by sodium methoxide in methanol and also in dimethyl sulfoxide (DMSO). That the anion of 3-hydroxypyridine was being formed was established by comparison with an authentic sample. The formation of methyl ether was established by mass spectrometry; this substance was distilled at 0° from a DMSO reaction mixture and characterized by its mass spectrum. It was possible to follow the disappearance of the methoxypyridine quantitatively using nmr because peaks of 3-hydroxypyridine anion are shifted upfield with respect to the starting material.

In principle, 3-methoxypyridine may undergo a cleavage reaction involving not only methoxide ion but also hydroxide ion.[5] Hydroxide ion is present in methanol–sodium methoxide when the methanol is not anhydrous[6] (eq 1). Since it is difficult to remove all

$$CH_3O^- + H_2O \rightleftharpoons CH_3OH + OH^- \quad (1)$$

traces of water from methanol, we attempted to determine whether hydroxide ion was responsible for a part of the cleavage. This was done using CD_3OD–CD_3ONa and CD_3OD–CD_3ONa–D_2O. Use of a deuterio rather than a proteo solvent makes it possible to employ nmr to identify cleavage products containing a methoxyl group. In proteo methanol signals for these products overlap with those of the solvent.

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(1) R. L. Burwell, *Chem. Rev.*, **54**, 615 (1954).

(2) E. Staude and F. Patat in "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience, New York, N. Y., 1967, Chapter 2.

(3) M. Forchiassin, G. Illuminati, and G. Sleiter, *J. Heterocycl. Chem.*, **6**, 879 (1969); C. Abbolito, C. Iavarone, G. Illuminati, F. Stegel, and A. Vazzoler, *J. Amer. Chem. Soc.*, **91**, 6746 (1969).

(4) L. Brandsma and J. F. Arens, in "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience, New York, N. Y., 1967, Chapter 13.

(5) Cleavage of 3-methoxypyridine by methoxide ion was first observed in our laboratory by Dr. Larry S. Helmick.

(6) J. Hine and M. Hine, *J. Amer. Chem. Soc.*, **74**, 5266 (1952).

Equations 2–7 give possible reactions between methoxypyridine and CD_3O^- and OD^-. In principle both of these oxide bases may react with the heterocyclic ether at either the saturated or ring carbon to give cleavage products. Reactions of methoxide-d_3 ion at

$$PyOCH_3 + CD_3O^- \longrightarrow PyO^- + CH_3OCD_3 \quad (2)$$

$$PyOCH_3 + CD_3O^- \longrightarrow PyOCD_3 + CH_3O^- \quad (3)$$

$$PyOCD_3 + CD_3O^- \longrightarrow PyO^- + CD_3OCD_3 \quad (4)$$

$$PyO^*CH_3 + OD^- \longrightarrow PyO^{*-} + CH_3OD \quad (5)$$

$$PyO^*CH_3 + OD^- \longrightarrow PyO^- + CH_3O^*D \quad (6)$$

$$PyOCD_3 + OD^- \longrightarrow PyO^- + CD_3OD \quad (7)$$

the saturated carbon are given in eq 2 and 4 and at the ring carbon in eq 3. Note that this latter reaction results in the formation of a new pyridyl methyl ether, one containing a CD_3O group; methoxy group exchange has taken place. Reaction of deuterioxide ion at the saturated carbon is given in eq 5 and at the ring carbon in eq 6, the symbol * serving to distinguish between the ether and deuterioxide ion oxygen atoms. Reaction of deuterioxide ion with the CD_3O ether in eq 7 may take place at the saturated or ring carbon.

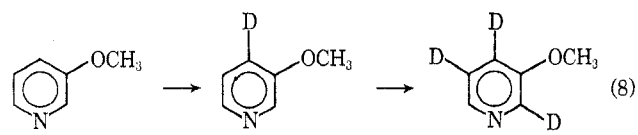
Reactions involving the methoxide ion may lead to methanol and methyl ether products while the deuterioxide (hydroxide) ion leads only to methanol. Each of these two products may be detected by nmr when CD_3OD serves as solvent; the latter peak was found to be 4.5 Hz downfield from the ether signal. However, quantitative analysis of each product is not possible, largely because signals lie within the multiplet of the residual CD_2HOD present in the solvent. Moreover, any CD_3OCD_3 and CD_3OD produced in reactions such as those in eq 4 and 7 are not measured by proton magnetic resonance.

The cleavage of 3-methyoxypyridine in CD_3OD–CD_3ONa was observed in two separate experiments. In the first no D_2O was added to the solvent. In the second 1.5 equiv (relative to the pyridine) of D_2O were added in order to ensure that the methanol was wet.

In both experiments at 164.7° as the signal of the methyl group of $PyOCH_3$ diminished, a signal due to CH_3OCD_3 appeared. No signal indicating the formation of CH_3OD could be detected, even after most of the substrate was consumed.

In order to show that the new signal appearing was due to CD_3OCH_3 and not to CH_3OD, the mixture was frozen in liquid nitrogen, the nmr tube opened, and CH_3OD injected in an amount corresponding to about 10% of the original quantity of heterocyclic ether. The nmr spectrum of this mixture clearly revealed the presence of the added methanol. Thus, even in the presence of added water no detectable reaction occurs between 3-methoxypyridine and deuterioxide ion. The stoichiometry of the ether cleavage reaction is given by eq 2.

The CD_3OD experiments also provide information about the ability of 3-methoxypyridine to deprotonate to give carbanions. Hydrogen–deuterium exchange was observed at positions 2, 4, and 5. That the most reactive site in 3-methoxypyridine is H-4 has been demonstrated.[7] H–D exchange at H-4 exceeds cleavage in rate but exchange at H-2 and H-5 is competitive with cleavage. Assignments of positions undergoing H–D exchange were based on chemical shifts and by changes in the spin coupling patterns.[8] Since substrate and base are consumed by ether cleavage, no attempt was made to obtain rate constants for hydrogen exchange. Rather, a rate constant ratio was obtained from a log–log plot of the percentage of hydrogen at H-5 *vs.* the percentage at H-2. Thus H-5 undergoes exchange 1.9 times as fast as H-2. Exchange was not observed at H-6. The order of introduction of deuterium into 3-methoxypyridine by means of methoxypyridyl anion formation is given in eq 8.



(8)

These H–D exchange results indicate that a methoxyl group exerts similar effects on the reactivity of ortho and meta positions. This is seen by comparison with H–D exchange data for pyridine. Under the same conditions pyridine undergoes H–D exchange at positions (H-3,5) meta to nitrogen 9.3 times as fast as at positions (H-2,6) ortho to nitrogen.[9] In 3-methoxypyridine a position (H-5) meta to both nitrogen and the methoxyl group is only 1.9 times as reactive as a position (H-2) ortho to both of these. That is, the effect of the ortho methoxy group is only 4.9 times as large as that of the meta methoxy group, assuming additivity of effects.

In proteo methanol only the cleavage of the ether linkage of 3-methoxypyridine is observable. Kinetic studies using CH_3OH–CH_3ONa were carried out under second-order conditions, CH_3ONa generally being in excess (Table I). Results from runs at two different base concentrations at 190.7° indicate that the second-order rate constant increases with increasing base concentration. This is not unexpected. Concentration is not the proper "acidity function" to be employed at high concentrations of methoxide ion.[10] Results from studies employing similar base concentrations at three temperatures give a linear Arrhenius plot; ΔH^* is

TABLE I

RATES OF CLEAVAGE OF PYRIDYL METHYL ETHERS BY SODIUM METHOXIDE

Substituted pyridine	Temp,[a] °C	Solvent	$[CH_3ONa]$,[b] M	10^4k_2, M^{-1} sec^{-1}
3-OCH_3	164.7	CH_3OH	0.968	0.47
3-OCH_3	190.7	CH_3OH	0.893	3.6
3-OCH_3	190.7	CH_3OH	0.488	2.2
3-OCH_3	218	CH_3OH	0.769	22.
3-OCH_3	164.7	CH_3OH–DMSO[c]	1.08[d]	6.4[d]
3-OCH_3	164.7	DMSO	Satd[e]	...[f]
4-OCH_3	164.7	CH_3OH	0.968	1.2
2-OCH_3	164.7	CH_3OH	0.968	0.42

[a] ±0.5°. [b] Corrected for thermal expansion. [c] 1:2.3 (v/v) CH_3OH–DMSO. [d] Uncorrected for thermal expansion. [e] Suspension of CH_3ONa in DMSO. [f] Pseudo-first-order rate constant is 5.6×10^{-4} sec^{-1}.

(7) I. F. Tupitsyn, N. N. Zatsepina, A. V. Kirova, and Yu. M. Kapustin, *Reakts. Sposobnost Org. Soedin.*, **5**, 243 (1968).

(8) For an illustration of the method, see J. A. Zoltewicz and G. M. Kauffman, *Tetrahedron Lett.*, 337 (1967).

(9) J. A. Zoltewicz, C. L. Smith, and G. Grahe, *J. Amer. Chem. Soc.*, **91**, 5501 (1969).

(10) C. H. Rochester, *Quart. Rev. (London)*, **20**, 511 (1966).

29.9 ± 1.1 kcal/mol and ΔS^* is −11 ± 2 eu. The negative entropy term also suggests an S_N2 mechanism.

Addition of dimethyl sulfoxide (DMSO) to the methanolic reaction mixture resulted in an increase in the rate of cleavage of 3-methoxypyridine by methoxide ion. In a 1:2.3 (v/v) mixture of CH_3OH–DMSO at 164.7° cleavage was about 14 times as fast as in neat methanol. Cleavage of this ether by sodium methoxide also was observed in neat DMSO. Rates of cleavage in the mixed solvent and in neat DMSO were essentially the same; the concentration of sodium methoxide in the mixed solvent was about 1 *M*. It is interesting to note that, although the sodium methoxide is not very soluble in DMSO, a good pseudo-first-order rate plot for cleavage was observed. We interpret this to mean that, in spite of the consumption of sodium methoxide in the cleavage reaction, essentially a constant concentration of this base is maintained in solution, provided that solid base is present. A suspension of sodium methoxide in DMSO appears to be a useful reagent for the cleavage of ethers. This mixture is an alternative to homogeneous CH_3ONa–CH_3OH.

2- and 4-methoxypyridine were cleaved by CH_3ONa–CH_3OH at 164.7°. That the anions of 2- and 4-hydroxypyridine[11] were products was determined by comparison with authentic materials. Rate constants are given in Table I.

The cleavage of 4-methoxypyridine was also studied in CD_3OD–CD_3ONa at 164.7° containing 1.5 equiv of added D_2O. Both CH_3OCD_3 and CH_3OD products were found. In addition considerable exchange of the methoxyl group of the pyridyl ether resulted. For example, the amounts of CH_3O, CD_3O, and DO (sodium salt) pyridine present at one point during the reaction were 26, 53, and 21%, respectively, and later 9, 58, and 33%. Methoxy group exchange is faster than ether cleavage. Because CH_3OD is liberated by methoxy group exchange (eq 3), we are unable to rule out the possible formation of this product by the action of OD^- (eq 5 and 6).

Our data on the cleavage of 3-methoxypyridine and on the reaction of 3-bromopyridine in methanol–water, described below, indicate that attack of hydroxide ion is not competitive with attack of methoxide ion on a saturated or an unsaturated carbon.[13] Note that this comparison involves both nucleophiles attacking carbon in the same state of hybridization. Whether cleavage of 4-methoxypyridine by hydroxide ion attack at the ring carbon is competitive with methoxide ion attack at the saturated carbon is not clear. The 2- and 4-methoxypyridines are likely to show similar reactivities toward both oxide ion nucleophiles.

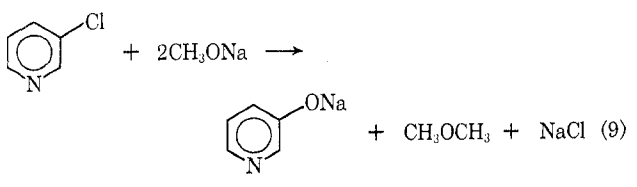
In general, it seems likely that in methanol–water mixtures some methyl aryl ethers may undergo cleavage by preferential reaction with the methoxide ion at the saturated carbon while others may undergo reaction with hydroxide ion at the unsaturated carbon, methoxide ion giving rise to methoxyl group exchange. Experiments similar to ours using CD_3OD may be useful to help determine the pathways being followed.

3-Methylthiopyridine in CH_3ONa–CH_3OH at 165° did not undergo detectable cleavage. Under the conditions employed, 3-methoxypyridine would have reacted completely. Thio ethers are said to be less reactive than their ether counterparts.[1,4]

Anisole underwent cleavage in 1 *M* CH_3ONa–CH_3OH at 218°; the reaction was essentially complete after 24 hr. Overlap of the phenolate ion protons with those of anisole precluded an accurate nmr kinetic study. Phenol was recovered in 70% yield as its 2,4,6-tribromo derivative after heating anisole at reflux in CH_3OH–CH_3ONa–DMSO. By contrast anisole is reported to be cleaved to a small degree in alcoholic KOH at 180–200°.[14] The facility of cleavage of the four methyl ethers investigated is 4-pyridyl > 3-pyridyl > 2-pyridyl > phenyl. For the 4-, 3-, and 2-methoxypyridines relative reactivity ratios at 164.7° are 2.8:1.1:1.0, respectively. This order qualitatively correlates with the acidity of the hydroxypyridines. Room temperature pK_a values are 7.80, 8.36, and 8.66, respectively.[15,16] Moreover, phenol is the least acidic of the four compounds considered and anisole is the least reactive ether.

3-Methylthiopyridine is less reactive than any of the three methoxypyridines although 3-mercaptopyridine with a pK_a = 4.8[17] is more acidic than any of the hydroxypyridines. However, the carbon affinity of sulfur is greater than the carbon affinity of oxygen.[18]

Consecutive Methoxy Dehalogenation and Ether Cleavage.—Comparison of our rate constant (2.2×10^{-3} M^{-1} sec^{-1}, 218°) for the cleavage of 3-methoxypyridine with that (5.1×10^{-4} M^{-1} sec^{-1}, 220°) reported for the formation of 3-methoxypyridine from 3-chloropyridine in methanol[19] suggested that the dehalogenation reaction was more complicated than previously realized. This comparison prompted us to attempt the conversion of 3-chloropyridine to 3-hydroxypyridine in CH_3ONa–CH_3OH according to eq 9. A 70% yield resulted. The reaction constitutes a convenient, one-



step conversion and appears to be superior to an older method giving low yields and employing a halopyridine, copper sulfate, and aqueous alkali.[20]

In view of these results a kinetic study was undertaken to redetermine the rate constant for methoxy dechlorination. Equimolar quantities of 3-chloropyridine and sodium methoxide were allowed to react at 218° and the reaction was followed by nmr. The

(11) Although 2- and 4-"hydroxy"-pyridines exist largely as their pyridone tautomers,[12] we employ the hydroxy nomenclature for the sake of clarity and emphasis. Cleavage of hydroxy derivatives are being considered.

(12) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **1**, 339 (1963).

(13) For additional information, see J. F. Bunnett and G. T. Davis, *J. Amer. Chem. Soc.*, **76**, 3011 (1954).

(14) R. Stoermer and B. Kahlert, *Chem. Ber.*, **34**, 1812 (1901).

(15) These values refer to dissociation of the hydroxypyridine tautomer.

(16) K. Schofield, "Hetero-Aromatic Nitrogen Compounds. Pyrroles and Pyridines," Plenum Publishing Co., New York, N. Y., 1967, pp 148, 152–154.

(17) This value refers to dissociation of the thiol tautomer.[16]

(18) J. Hine and R. D. Weimar, Jr., *J. Amer. Chem. Soc.*, **87**, 3387 (1965).

(19) M. Liveris and J. Miller, *J. Chem. Soc.*, 3486 (1963).

(20) H. Maier-Bode, *Chem. Ber.*, **69**, 1534 (1936).

H-2,6 multiplets of 3-chloro- and 3-methoxypyridine and the H-4,5 multiplets of the anion of 3-hydroxypyridine are clearly separated from other aromatic ring hydrogen signals. The centers of these multiplets are ound at τ 1.5, 1.8, and 3.1, respectively. This favorable situation allowed the concentrations of all pyridine species to be determined as a function of time. The results shown in Figure 1 indicate that 3-chloropyridine is converted to 3-methoxypyridine which in turn reacts to yield the anion of 3-hydroxypyridine. The concentrations of chloropyridine and hydroxypyridine anion tend toward a common value. This is estimated to be 38% of the initial pyridine concentration. The amount of methoxypyridine rises to a maximum of about 28% and then decreases to about 24%.

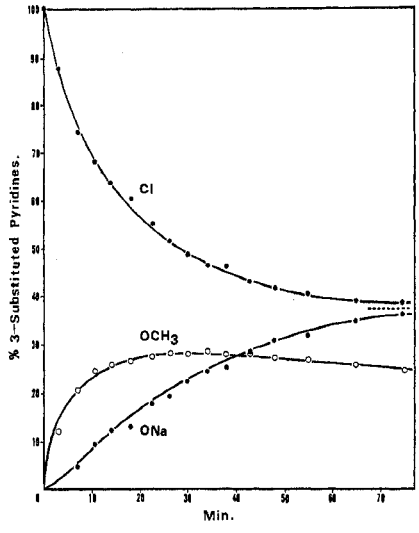


Figure 1.—Plots of the molar percentages of 3-substituted pyridines in the reaction of 3-chloropyridine with sodium methoxide in methanol at 218° as a function of time. Concentrations of starting material, 3-methoxypyridine intermediate, and the sodium salt of 3-hydroxypyridine were followed by nmr. Reactants were present initially at the same concentration, 0.381 M. The dashed line indicates a limiting value.

This concentration–time dependence is characteristic of a reaction system consisting of two competitive, consecutive, irreversible, second-order reactions. It is to be noted that when equimolar quantities of two starting materials A and B are employed, starting material A and a product resulting at the end of the two-step sequence approach the same limiting concentration as reactant B is consumed. Moreover, the maximum amount of intermediate formed is independent of the relative concentrations of reactants used.

Knowing the concentration ratios in the consecutive reactions, it is possible to obtain the rate-constant ratio for the two reactions. Two different methods were employed;[21,22] both gave essentially the same results. At 218° methoxy dechlorination of 3-chloropyridine has a second-order rate constant which is 0.53 times as large as that for cleavage of 3-methoxypyridine by methoxide ion. Since the ether cleavage rate constant was determined separately (Table 1), the rate constant for dechlorination is calculated to be $1.2 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$.

Treating the reaction of 3-chloropyridine with CH_3ONa–CH_3OH as a simple second-order reaction generates a curved rate plot. However, a linear region corresponding to about 50% reaction of the chloropyridine does result. This portion of the plot gives a rate constant, $1.0 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$, in good agreement with that obtained from the consecutive reaction treatment above. Our value is about twice as large as the previously reported value.[19] This may be due in part to the relative weight given to the points in constructing a second-order plot; the points later in the reaction giving rise to a smaller apparent constant. Salt effects may be another factor, since different salt concentrations were employed.

The reaction of 3-bromopyridine with CH_3ONa–CH_3OH at 218° also gave rise to 3-methoxypyridine and the anion of 3-hydroxypyridine. When equimolar amounts of the initial reactants were employed, the concentration of 3-bromopyridine and the anion of 3-hydroxypyridine tended to a limiting value of 35%. The concentration of 3-methoxypyridine rose to a maximum of 32% and then decreased to about 30%. The rate constant ratio of the first to the second reaction is 0.75. Hence, the rate constant for methoxy debromination is 40% as large as that for methoxy dechlorination (Table II). This result indicating a lack of an "element effect" in the dehalogenation reactions is good evidence for the expected aromatic, nucleophilic substitution mechanism.[23]

TABLE II

KINETICS OF METHOXY DEHALOGENATION OF 3-HALOPYRIDINES IN METHANOL AT 218°

Halogen[a]	$[CH_3ONa]$,[b] M	10^3k, M^{-1} sec^{-1}
Cl	0.381	1.2
Br	0.433	1.7

[a] Same concentration as sodium methoxide. [b] Corrected for thermal expansion.

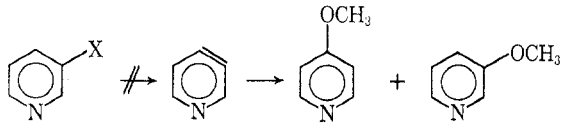
Curiously, 3-bromopyridine and methanolic KOH are reported to give 3-methoxypyridine in 87% yield but experimental details are lacking.[24] In an attempt to repeat this at 165° using a 5% excess of potassium hydroxide in methanol we found the amount of 3-methoxypyridine to rise to a maximum value of 36% after 9 hr and then decrease. The hydroxypyridine anion was the other product and was present to a lesser extent than the methoxypyridine. Note that these results show that the rate of hydroxide ion attack at the unsaturated carbon is less than the rate for methoxide ion.[13]

Noteably methoxy dehalogenation of 2- and 4-chloropyridines occurs rapidly enough so that ether cleavage is not a serious side reaction.[19]

Our results also eliminate 3,4-pyridyne[25] formation

(21) P. R. Wells, *J. Phys. Chem.*, **63**, 1978 (1959).
(22) W. G. McMillan, *J. Amer. Chem. Soc.*, **79**, 4838 (1957).
(23) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *ibid.*, **91**, 6746 (1969).
(24) E. Koenigs, H. C. Gerdes, and A. Sirot, *Chem. Ber.*, **61**, 1022 (1928).
(25) For reviews, see T. Kaufmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 543 (1965); H. J. den Hertog and H. C. van der Plas, *Advan. Heterocycl. Chem.*, **4**, 121 (1965).

(eq 10) and halogen transfer,[26] as serious competing reactions of 3-halopyridines with sodium methoxide.



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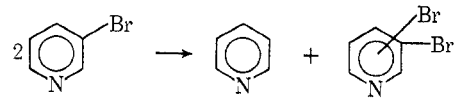

(11)

Although the 4 anions of 3-halopyridines are formed in CH_3ONa–CH_3OH,[32] there is no evidence among the reaction products of 3,4-pyridyne formation. All of the pyridine components present in the reaction mixture are accountable in terms of 3-halo-, 3-methoxy-, and the anion of 3-hydroxypyridine to within an uncertainty of about 7%. This was determined by nmr using *tert*-butyl alcohol as a reference standard. This uncertainty reflects the combined uncertainty in the four nmr measurements. Moreover, 3- and 4-methoxypyridines are expected to result from the reactions of 3,4-pyridyne (eq 10). These ethers would undergo cleavage as well. If the anion of 4-hydroxypyridine were formed, it would have been detected among the substituted pyridines, using its H-3,5 signals centered at τ 3.6. Signals at this chemical shift were not detected during the reactions of 3-halopyridines. Moreover, the H-2,6 signals of pyridine, a product of halogen transfer, also could not be detected. Since these pyridine signals overlap with those of halopyridine starting material, removal of the halopyridine was required. This was achieved when excess sodium methoxide was employed. Thus our experiments set an upper limit of about 7% to the degree of 3,4-pyridyne formation and to halogen transfer which might occur during the reactions of 3-chloro- and 3-bromopyridine with CH_3ONa–CH_3OH at 218°.

In summary, pyridyl methyl ethers are cleaved by methoxide ion in an S_N2 reaction. Methoxy dehalogenations of 3-halopyridines are complicated by this cleavage reaction.[32a]

Experimental Section

Materials.—Anisole, 2-methoxy- and 3-hydroxypyridine, and 2- and 4-pyridone were commercially available. Methanol-d_4 containing about 0.5% CD_2HOD was obtained from Merck Chemical Division. 3-Thiomethoxy-[33] and 3-[34] and 4-methoxypyridine[35] were prepared. Methanol was dried by distillation from magnesium methoxide, *tert*-butyl alcohol from potassium *tert*-butoxide. Sodium methoxide solutions were prepared by dissolving freshly cut sodium in dry methanol under dry nitrogen; solutions were standardized as before.[36] Dimethyl sulfoxide was dried over molecular sieves. Solutions were protected from air by serum stoppers and transfers were made by syringe.

Cleavage of Anisole by Sodium Methoxide in Methanol–DMSO.—To a mixture of 10 ml of methanol and 40 ml of dimethyl sulfoxide were added 5.4 g (0.050 mol) of anisole and 5.4 g (0.1 mol) of commercial powdered sodium methoxide. After heating at reflux for 18 hr, the solution was concentrated at atmospheric pressure to 0.5 volume and then diluted with water and acidified with hydrochloric acid. The filtered solution was treated with aqueous bromine and the phenol was isolated as 2,4,6-tribromophenol (12 g, 70%), mp 93–95° (lit.[37] mp 95–96°).

Preparation of 3-Hydroxypyridine from 3-Chloropyridine and Sodium Methoxide–Methanol.—A mixture of 1.2 g (0.0094 mol) of 3-chloropyridine and 20 ml of a saturated solution of sodium methoxide in methanol was heated in a metal bomb at 230° (metal bath temperature) for 4 hr. On cooling, the mixture was carefully diluted with water, neutralized with dilute hydrochloric acid, and evaporated under reduced pressure to a small volume. 3-Hydroxypyridine was recovered by filtration. Evaporation of the mother liquor to dryness and extraction of the residue with acetone gave a further crop; the combined yield of 3-hydroxypyridine, mp 126–128° (lit.[38] mp 124.5°), was 0.60 g (70%).

Kinetic Procedure. I. Cleavage of Methoxypyridines by Sodium Methoxide.—The reaction solution for a typical run was prepared by syringing aliquots of sodium methoxide, *tert*-butyl alcohol reference compound, dimethyl sulfoxide for mixed solvents runs, and the methyl ether into a 2-ml volumetric flask and diluting to mark with dry methanol. In the case of neat dimethyl sulfoxide, excess powdered sodium methoxide was employed. Ether concentrations were generally 0.3–0.4 *M* after mixing. An aliquot of this solution was placed into a nitrogen-filled nmr tube which was then sealed. After an nmr spectrum was obtained, the tube was suspended in a constant-temperature vapor bath (mesitylene, 164.7°; benzonitrile, 190.7°; naphthalene, 218°). The spectrum of the cooled sample was obtained on a Varian A-60A spectrometer and integrated.

The ratio of the areas of the H-2,6 peaks of 3- and 4-methoxypyridine and the H-6 peaks of the 2-methoxypyridine to the area of the reference compound provides a measure of the extent of reaction. These signals of the ether reactant do not overlap with signals from the product. Ratios used in plots were based on an average of six or more integration sweeps, caution being taken to avoid saturation effects.

When the methoxide ion concentration exceeded the ether concentration, kinetic plots were constructed by plotting the logarithm of $[CH_3ONa]/[PyOCH_3]$ against time. Second-order constants were obtained from the slope of the best visual line through the points. Good straight lines were obtained.

When the initial concentrations of methoxide ion and ether were the same, the nmr area ratios of standard to substrate were plotted against time.

Concentrations are corrected for thermal expansion by multiplying concentrations at room temperature by the ratio of the density of methanol at the reaction temperature to that at room temperature.[39] Results are given in Table I.

The amount of sodium methoxide consumed during kinetic runs was determined by titration. To an aliquot of a reaction mixture was added 2.00 ml of 0.999 *M* hydrochloric acid. The acidic solution then was potentiometrically titrated with 0.195 *M* sodium hydroxide. Three equivalence points were observed. The first due to titration of excess hydrochloric acid, the second to pyridinium ions, and the third to hydroxypyridine. The equivalence point for the latter was not sharp, however. From

(26) Halogen transfer has been observed to take place in pyridines,[27] benzenes,[28] thiophenes,[29] isothiazoles,[30] and imidazoles,[31] amide ion frequently serving as a catalyst. Bromine atom transfer is faster than transfer of a chorine atom.

(27) M. J. Pieterse and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **81**, 855 (1962).

(28) C. E. Moyer, Jr., and J. F. Bunnett, *J. Amer. Chem. Soc.*, **85**, 1891 (1963); J. F Bunnett and D J. McLennan, *ibid.*, **90**, 2190 (1968).

(29) M. G. Reinecke and H. W. Adickes, *ibid.*, **90**, 511 (1968); S. Gronowitz and B. Holm, *Acta Chem. Scand.*, **23**, 2207 (1969).

(30) D. A. deBie and H. C. van der Plas, *Tetrahedron Lett.*, 3905 (1968).

(31) D. A. deBie and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **88**, 1246 (1969).

(32) J. A. Zoltewicz and C. L. Smith, *Tetrahedron*, **25**, 4331 (1969).

(32a) NOTE ADDED IN PROOF.—A useful method of cleaving substituted anisoles involves thioethoxide ion in *N*,*N*-dimethylformamide: G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1327 (1970). 1-Ethyl-2-methoxy-5-nitropyridinium salts undergo ether cleavage reactions with a variety of nucleophiles: T. Severin, D. Bätz, and H. Lerche, *Chem. Ber.*, **103**, 1 (1970).

(33) J. A. Zoltewicz and C. Nisi, *J. Org. Chem.*, **34**, 765 (1969).

(34) D. A. Prins, *Recl. Trav. Chim. Pays-Bas*, **76**, 58 (1957).

(35) E. Spinner and J. C. B. White, *Chem. Ind. (London)*, 1784 (1967).

(36) J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.*, **34**, 1405 (1969).

(37) "Handbook of Chemistry and Physics," R. C. Weast, S. M. Selby, and C. D. Hodgman, Ed., 46th ed, Chemical Rubber Co., Cleveland, Ohio, 1965, p c-470.

(38) O. Fischer and E. Renouf, *Chem. Ber.*, **17**, 1896 (1884).

(39) J. Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Vol. I, Elsevier, New York, N. Y., 1950, p 303.

these data and the degree of ether cleavage it is possible to calculate the amount of sodium methoxide remaining prior to acidification. Concentrations agreed to within a few per cent of expected values, assuming the stoichiometry of eq 2.

The methods employed to investigate ether cleavage reactions in CD_3OD–CD_3ONa were similar to those employed when the solvent was proteo methanol. In the case of 4-methoxypyridine, methoxy group exchange was observed. The extent of this exchange was determined by comparison of the nmr area of the CH_3O group in the pyridyl ether with the H-2,6 area of this ether. The H-2,6 area provides a measure of CH_3O and CD_3O substrate while the CH_3O signal provides a measure of substrate not having undergone methoxyl group exchange. Even though hydrogen–deuterium exchange does take place at H-3,5 of 4-methoxypyridine, none was detected at H-2,6. The combined areas of H-2,6 of 4-methoxypyridine and of H-2,6 of the anion of 4-hydroxypyridine relative to added *tert*-butyl alcohol internal standard were constant throughout ether cleavage and hydrogen exchange.

II. 3-Chloro- or 3-Bromopyridine and Sodium Methoxide–Methanol. Consecutive, Competing Reactions.—Methods were similar to those given above with the following modifications. Equimolar quantities (Table II) of halopyridine and methanolic sodium methoxide were heated at 218° in sealed nmr tubes. The disappearance of the halo compound was followed by observing its H-2,6 signals centered at τ 1.5, the 3-methoxypyridine H-2,6 signals at τ 1.8 and the H-4,5 signals of the anion of 3-hydroxypyridine centered at τ 3.1. *tert*-Butyl alcohol τ 8.8 served as a reference standard.

The sum of the nmr areas at τ 1.5, 1.8, and 3.1 provides a measure of the total amount of the three pyridines and the ratio of one of the three areas to the total represents the fractional amount of that pyridine present. In Figure 1 these fractions, as percentages, are given as a function of time for the chloropyridine reaction. Similar curves were obtained for the bromopyridine reaction. Some difficulty was encountered with nmr determinations of the chloro reaction mixture, owing to the precipitation of NaCl. Vigorous shaking of the sample tube prior to determinations proved to be beneficial. Sodium bromide was soluble at ambient temperatures.

3-Halopyridine, 3-methoxypyridine, and the anion of 3-hydroxypyridine approach limiting concentrations as the concentration of sodium methoxide tends to zero. For the 3-chloropyridine the limiting percentages are estimated to be 38, 24, and 38, respectively. For 3-bromopyridine these percentages are 35, 30, and 35, respectively.

The ratio of the second-order rate constants for methoxy dehalogenation and methyl ether cleavage was estimated in two ways, the method of Wells[21] employing concentration ratios at the end of the reaction and the method of McMillan[22] employing concentration ratios for arbitrary degrees of reaction. Both methods gave results in agreement. For 3-chloropyridine the ratio of the rate constants for methoxy dehalogenation and ether cleavage is 0.53, for 3-bromopyridine 0.75. Thus, methoxy debromination is about 40% faster than methoxy dechlorination. It is to be noted that the sodium halide is incompletely soluble at the reaction temperature.

In a control experiment 3-methoxypyridine was heated with NaCl in methanol at 218°. After 10 hr some 28% of the methoxypyridine had reacted but no attempt was made at characterization. Note that in the above kinetic experiments the reaction time did not exceed 90 min.

Registry No.—2-Methoxypyridine, 1628-89-3; 3-methoxypyridine, 7295-76-3; 4-methoxypyridine, 620-08-6; sodium methoxide, 124-41-4; anisole, 100-66-3; 3-chloropyridine, 626-60-8; 3-bromopyridine, 626-55-1.

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Basicities and H–D Exchange of Pyrazine N-Oxides

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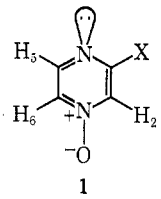
The hydrogen–deuterium exchange rates of H_2 and H_6 in some 3-substituted pyrazine 1-oxides have been correlated with σ constants, and the log of the H_2 exchange rates have been shown to be linearly related to the pK_a's of these compounds. The implication of these results upon the intermediacy of an ylide-like intermediate are discussed.

Base-catalyzed H–D exchange in pyridine N-oxide, its 3-chloro- and 3,5-dichloro derivatives have recently been described by Zoltewicz and Kauffman.[1,2] These studies showed that the 2,6 positions exchange more rapidly than the 3,5 positions, which in turn are more susceptible to H–D exchange than the 4 position. Similar, but qualitative, studies on pyridazine N-oxides showed that the protons undergo stepwise deuteration at the 6, 5, 4, and finally at the 3 position.[3]

We now wish to report the base-catalyzed H–D exchanges of the parent and of some substituted pyrazine N-oxides initiated with the aim of elucidating the effects that an additional heteroatom and different ring substituents have upon these exchange processes.

The considerable exchange-rate enhancement caused by replacement of the $=C_4-H$ function in a pyridine N-oxide by a $=N_4$ (formation of a pyrazine N-oxide) is evident from the following observations: The proton α to the N-oxide and chloro groups (H_2) in 3-chloropyrazine 1-oxide exchanges with a half-life of approximately 4 min, at 31° and in 0.0025 N NaOD. This compares with a half-life of 40 min for the exchange of H_2 in 3-chloropyridine N-oxide under more severe conditions (0.045 N NaOD and at 74°).

Because of the facility with which the pyrazine N-oxides undergo H–D exchange, they lend themselves admirably to this type of study. Furthermore, the presence of the additional heteroatom in these compounds (N_4) offers an "internal" reference standard with respect to the effect that a substituent (X in structure **1**) has upon the σ C_2–H bond in comparison with the similarly placed lone pair of electrons on N_4.



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(1) J. A. Zoltewicz and G. M. Kauffman, *Tetrahedron Lett.*, 337 (1967).
(2) J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.*, **34**, 1405 (1969).
(3) Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull.*, **12**, 1384 (1964).