

variable-temperature accessory, was used to record esr spectra. Computer-simulated spectra were obtained using a computer program written by Griffin.<sup>38</sup> ESR spectra recorded at room temperature were produced from solutions electrolyzed in a Varian E-3 electrochemical cell under oxygen-free nitrogen. At low temperatures, radicals were electrolytically generated in an esr vacuum cell designed by Holz<sup>39</sup> and modified by Rieke and Rich.<sup>40</sup> The cell was degassed by five freeze-pump-thaw cycles before sealing and could maintain a vacuum of at least  $10^{-3}$  Torr for the duration of the experiment. A silver bead reference electrode was used in the cell.

Standard three-electrode operational amplifier circuitry was used. All electrical measurements are *vs.* the saturated sodium chloride colomel reference electrode (SSCE) and are uncorrected for junction potentials. The cell design and instrumentation

(38) B. Griffin, Ph.D. Thesis, Washington University, St. Louis, Mo., 1968.

(39) J. Holtz, Ph.D. Thesis, Yale University, New Haven, Conn.

(40) R. D. Rieke and W. E. Rich, *J. Amer. Chem. Soc.*, **92**, 7349 (1970).

have been described previously.<sup>37</sup> In a typical experiment, solutions containing  $1 \times 10^{-3}$  M **1a** and 0.1 M TBAH were studied electrochemically at a platinum electrode in any oxygen-free nitrogen atmosphere.

The apparatus for flash spectroscopic studies has been described<sup>2</sup> previously. Samples for flash photolysis were  $1 \times 10^{-4}$  M and were degassed by five freeze-pump-thaw cycles.

Zinc reductions were carried out under vacuum by exposing a  $1 \times 10^{-3}$  M solution of **1a** to a freshly distilled zinc mirror.

**Registry No.**—*trans-1b* (tetrafluoroborate), 34247-36-4; 1,2-bis(4-pyridyl)ethylene diethyl iodide radical cation, 34195-73-8.

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## The Mechanism of Nucleophilic Substitution of N-Methyl-4-Substituted Pyridinium Salts<sup>1</sup>

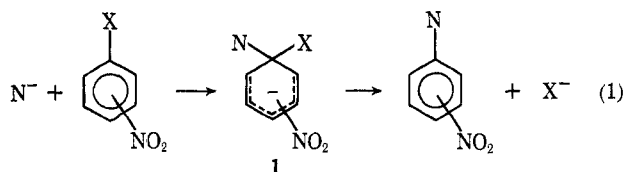
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Rates and activation parameters have been determined for the reaction of sodium hydroxide in aqueous solution with *N*-methyl-4-halopyridinium salts and *N*-methyl-4-methoxypyridinium fluoroborate. The results obtained indicate that the mechanism is similar to the mechanism of nucleophilic displacement which occurs with halogenated nitrobenzenes.

Nucleophilic aromatic substitution of halogenated nitrobenzenes is a well-understood process.<sup>2-9</sup> The reaction occurs by a two-step mechanism (eq 1) and is

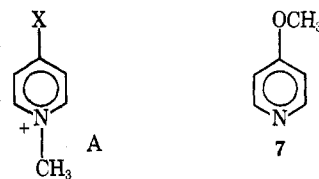


significantly different from nucleophilic substitution at saturated centers in a number of respects. (1) The transition state is characterized by little or no carbon-halogen bond breaking. (2) The reactivity of various halogens is related to their inductive effects, rather than to their bond strengths. (3) The reaction proceeds *via* a Meisenheimer complex intermediate (**1**).<sup>10</sup>

Nucleophilic displacements in heteroaromatic systems have been studied much less thoroughly than those in the benzene system. *N*-alkyl pyridinium salts undergo nucleophilic displacement much more readily than do the corresponding *N*-oxides, which in turn react more readily than do the corresponding unsub-

stituted compounds.<sup>11</sup> Meisenheimer-type complexes have been isolated from the reactions of a number of pyridine compounds.<sup>12</sup> However, it is not clear to what extent the mechanism in the pyridine series is like that of the benzene series.

The purpose of the present study was to obtain kinetic data for nucleophilic displacement reactions of compounds **2-7** in order to make comparisons with the



**2**, X = F; A = I<sup>-</sup>

**3**, X = Cl; A = I<sup>-</sup>

**4**, X = Br; A = BF<sub>4</sub><sup>-</sup>

**5**, X = I; A = BF<sub>4</sub><sup>-</sup>

**6**, X = OCH<sub>3</sub>; A = BF<sub>4</sub><sup>-</sup>

corresponding nitro and dinitrobenzene compounds. From these data we hope to determine the extent to which the reaction mechanism in the pyridine series is similar to that in the benzene series.

## Results

Rates of reaction of compounds **2-6** with hydroxide ion in aqueous solution at several temperatures are summarized in Table I. All measurements were carried out spectrophotometrically under pseudo-first-

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(12) P. Bemporad, G. Illuminati, and F. Stegel, *J. Amer. Chem. Soc.*, **91**, 6742 (1969).

(1) This research was supported by Grant NS 07657 from the National Institutes of Health.

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(3) J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).

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(9) R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.*, **6**, 229 (1966).

(10) M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969).

TABLE I  
RATES OF REACTION OF 4-SUBSTITUTED *N*-METHYLPYRIDINIUM  
SALTS WITH SODIUM HYDROXIDE IN WATER

Compd	Temp, °C	$k, M^{-1} \text{sec}^{-1}$ ( $\times 10^4$ ) <sup>a</sup>
2	40.2	77,400
	30.0	36,100
	20.5	18,100
	15.2	11,500
3	40.0	376
	30.0	150
	20.1	60.2
	10.0	19.8
4	39.0	284
	30.0	131
	20.1	48.6
	10.0	16.2
5	45.9	217
	37.6	100
	30.0	52.9
	18.0	16.4
6	40.7	57.0
	30.0	20.0
	20.0	7.59
	10.0	2.34

<sup>a</sup> Rate constants are the average of three runs at constant ionic strength.

order conditions at ionic strength 0.1. The concentration of pyridinium salt was about  $10^{-5} M$ . Each reported rate constant is a composite of three measurements made over a twofold range of hydroxide concentrations. The kinetic data were fitted to the usual first-order rate law using the nonlinear least-squares program of Taylor and Williams.<sup>13</sup> All reactions followed good second-order kinetics, first order in hydroxide and first order in pyridine.

The rate of hydrolysis of **6** is very sensitive to ionic strength. Increasing the ionic strength from 0.076 to 0.15 resulted in a decrease in the observed second-order rate constant from  $7.82 M^{-1} \text{sec}^{-1}$  to  $7.23 M^{-1} \text{sec}^{-1}$ . For this reason all kinetic measurements were made at constant ionic strength.

Beak, Bonham, and Lee<sup>14</sup> have shown that under certain conditions **6** is susceptible to nucleophilic attack on a methyl group, forming either 4-methoxypyridine or *N*-methyl-4-pyridone. We thus deemed it essential to determine whether reaction of this compound with hydroxide occurs on the ring or on the methyl group. The hydrolysis was carried out at 70° for 4 hr in aqueous 0.1 *M* sodium hydroxide containing 23 atom % <sup>18</sup>O. The product *N*-methyl-4-pyridone was isolated and analyzed by mass spectrometry. It contained 23 atom % <sup>18</sup>O. Thus displacement occurs primarily on the ring, although we cannot exclude the possibility of a small amount of displacement on the methyl group.

The rate constants in Table I were used to calculate the activation parameters shown in Table II. In all cases an excellent fit to the usual equation was obtained by the method of least squares.<sup>15</sup>

Several attempts were made to measure the rate of reaction of 4-methoxypyridine (**7**) with hydroxide ion

TABLE II  
ACTIVATION PARAMETERS FOR  
4-SUBSTITUTED *N*-METHYLPYRIDINIUM SALTS<sup>a</sup>

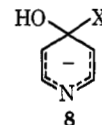
Compd	$\Delta H^*$ , kcal/mol	$\Delta S^*$ , cal/deg mol
2	13.0	-13.0
3	16.6	-12.1
4	16.8	-11.8
5	16.4	-15.0
6	17.7	-12.6

<sup>a</sup> Calculated using a standard least-squares method from rate constants at four different temperatures.

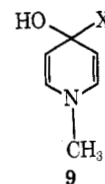
in water. However, no reaction was observed in 43 days at 25°. Assuming that we might have missed 1% reaction, an upper limit of  $1.2 \times 10^{-8} M^{-1} \text{sec}^{-1}$  can be placed on the rate constant.

### Discussion

4-Methoxypyridine and 4-chloropyridine are extremely unreactive toward nucleophilic displacement. The aza function in **8**, the anticipated intermediate,



is ineffective in supporting a negative charge, and reaction occurs only very slowly. On the other hand, 4-substituted *N*-methylpyridines are quite reactive, being similar in reactivity to substituted 2,4-dinitrobenzenes, and more than a millionfold more reactive than 4-substituted pyridines. The intermediate which is presumably formed in this case, **9**, is sufficiently stable



that numerous examples of this structure are known.<sup>16</sup> The high sensitivity of the hydrolysis reaction to ionic strength is consistent with the occurrence of intermediate **9**, although a similar dependence on ionic strength would be expected if **9** were a transition state, rather than an intermediate.

The variation in hydrolysis rate of 4-substituted *N*-methylpyridinium salts with the nature of the leaving group is similar to that encountered in the benzene series<sup>17-19</sup>—the fluoro compound is the most reactive by more than two orders of magnitude, and methoxide is about as good a leaving group as iodide. However, the rate variation is quite unlike that encountered in concerted displacements. The similarity between the pyridine series and the benzene series is striking. In Figure 1 are plotted rate constants for the reaction of the various pyridine compound with hydroxide *vs.* the rate constants for the reaction of the corresponding dinitrobenzene compounds with methoxide. The ex-

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(15) F. Daniels and R. A. Alberty, "Physical Chemistry," Wiley, New York, N. Y., 1963, p 650.

(16) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, pp 303-330.

(17) K. C. Ho, J. Miller, and K. W. Wong, *J. Chem. Soc. B*, 310 (1966).

(18) A. L. Beckwith, J. Miller, and C. D. Leahy, *ibid.*, 3552 (1952).

(19) J. H. Fendler, *J. Amer. Chem. Soc.*, **88**, 1237 (1966).

cellent straight line which is obtained is further evidence that aromatic nucleophilic substitution in *N*-substituted pyridines occurs by a mechanism very similar to that of the substituted nitrobenzenes.

The entropies of activation for compounds 2-6 show no significant trend. Only the iodo compound differs appreciably from the others. The larger  $\Delta S^\ddagger$  in this case is presumably a result of van der Waals repulsion between the bulky iodine and the nucleophile. Significantly, the entropies of activation are more than 15 eu more positive than those observed in the benzene series, presumably because the transition state in the pyridine series is much less polar than the ground state, and is therefore less solvated. Except for the iodo compound, the rates of reaction of the substituted pyridines with hydroxide closely parallel the activation enthalpies.

We conclude that the mechanism of nucleophilic displacement in 4-substituted *N*-methylpyridinium salts is strikingly similar to the mechanism of nucleophilic displacement of halonitrobenzenes.

### Experimental Section

All melting points are uncorrected. All compounds gave satisfactory elemental analyses and had nmr, ir, and uv spectra consistent with the assigned structures.

**Materials.**—4-Methoxypyridine and 4-chloro-*N*-methylpyridinium iodide were prepared by standard methods.<sup>20,21</sup>

4-Methoxy-*N*-methylpyridinium tetrafluoroborate was prepared in a manner similar to that of Beak and Bonham.<sup>22</sup> 4-Methoxypyridine (7.9 g) was dissolved in 150 ml of ethylene chloride, and 12.3 g of AgNO<sub>3</sub> and 40 ml of CH<sub>3</sub>I were added. The mixture was stirred at room temperature overnight. The yellow product was recrystallized from methanol-acetone-ether, yield 10.9 g (60%), mp 141.5-142.5°. *Anal.* Calcd: C, 33.45; H, 4.01; N, 5.58; I, 50.54. Found: C, 33.50; H, 4.01; N, 5.70; I, 50.83. The tetrafluoroborate salt was prepared by mixing equimolar amounts of 4-methoxy-*N*-methylpyridinium iodide and AgBF<sub>4</sub> in CH<sub>3</sub>OH; the white solid obtained was recrystallized from acetone-ether, mp 56-57° (lit. mp 56-58). *Anal.* Calcd: C, 39.85; H, 4.78; N, 6.64. Found: C, 39.90; H, 4.77; N, 6.80.

4-Bromo-*N*-methylpyridinium tetrafluoroborate was prepared by a method similar to that used by Berson, *et al.*<sup>23</sup> 4-Bromopyridine (prepared by neutralizing 10 g of the hydrochloride with Na<sub>2</sub>CO<sub>3</sub> in ether with 1% H<sub>2</sub>O and drying with MgSO<sub>4</sub>) was treated with CH<sub>3</sub>I (24 ml) in the presence of AgBF<sub>4</sub> (10 g) at 0° for 18 hr in the dark. The product was precipitated with ether and recrystallized twice from methanol-ether, yield 6.5 g (63.2%), mp 110.5-111.5°. *Anal.* Calcd: C, 27.73; H, 2.72; N, 5.39; Br, 30.75. Found: C, 27.61; H, 2.70; N, 5.41; Br, 30.57.

4-Fluoro-*N*-methylpyridinium iodide was prepared by a method similar to that used by Finger.<sup>24</sup> 4-Chloro-*N*-methylpyridinium iodide (2.56 g) was treated with dry KF (2 g) in DMF at 55° for 14 hr. The product was precipitated by addition of ether and recrystallized from DMF-ether and then from methanol-acetone-ether, yield 2.3 g (96.2%), mp 181-182°. *Anal.* Calcd: C, 30.15; H, 2.95; N, 5.86. Found: C, 29.99; H, 2.91; N, 5.79.

(20) L. Haitinger and A. Lieben, *Monatsh. Chem.*, 320 (1885).

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(22) P. Beak and J. Bonham, *ibid.*, **87**, 3365 (1965).

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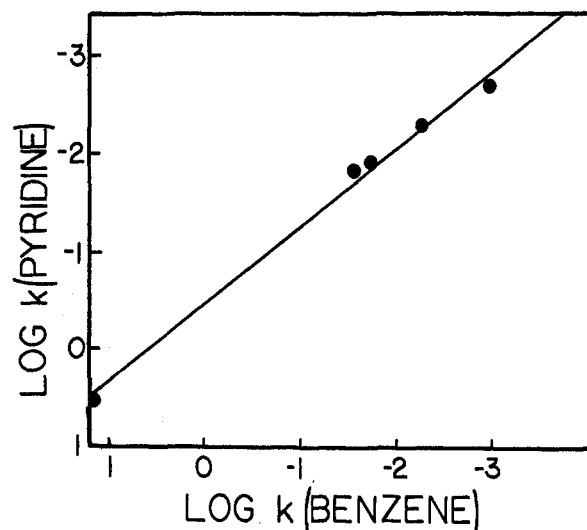


Figure 1.—Rates of reaction of 4-substituted *N*-methylpyridinium salts with hydroxide in water at 30° vs. rates of reactions of 1-substituted 2,4-dinitrobenzenes with methoxide in methanol at 25° (data from ref 17-19).

4-Iodo-*N*-methylpyridinium tetrafluoroborate was prepared by a method similar to that used by Finger.<sup>24</sup> 4-Bromo-*N*-methylpyridinium tetrafluoroborate (2.0 g) was treated with dry NaI (14 g) in dimethyl sulfoxide at 130° for 3 hr. The product, 4-iodo-*N*-methylpyridinium iodide, was precipitated by addition of ether. The tetrafluoroborate salt was prepared by treatment of the iodide with 1 equiv of AgBF<sub>4</sub> in aqueous solution. After removal of water, the product was recrystallized from acetone-ether, yielding 1.87 g (70%), mp 151.5-153.5°. *Anal.* Calcd: C, 23.49; H, 2.30; N, 4.56. Found: C, 23.71; H, 2.34; N, 4.53.

All other materials were reagent grade. Water was deionized and then twice distilled in an aged all-glass apparatus.

**Kinetics.**—Kinetic measurements were made by observing the increase in absorption at 259-265 nm of *N*-methyl-4-pyridone on a Gilford Model 222 recording spectrophotometer. For the 20 and 10° runs of 6, and for the 10° runs of 3 and 4, the kinetics were followed by taking aliquots from a 100-ml volumetric flask containing the standard hydroxide solution and approximately 10<sup>-5</sup> *M* of the appropriate pyridinium salt, and quenching with 1 ml of 2 *M* acetic acid. Kinetics at all other temperatures were conducted in a Teflon stoppered 3-ml uv cell. Infinity points were taken after 10 half-lives. NaClO<sub>4</sub> was used to maintain constant ionic strength. The temperature control was  $\pm 0.05^\circ$ . The uv spectrum of the product was always identical with that of *N*-methyl-4-pyridone.

**Isotopic Experiments.**—4-Methoxy-*N*-methylpyridinium tetrafluoroborate was treated with potassium hydroxide in water containing 23 atom % <sup>18</sup>O at 70° for 4 hr. Water was removed by lyophilization, a small amount of 0.1 *M* HCl was added, and the product was dissolved in CHCl<sub>3</sub>. The mass spectrum taken after evaporation of the solvent was identical with that of *N*-methyl-4-pyridone except for the presence of a peak at *m/e* 111 corresponding to *N*-methyl-4-pyridone-<sup>18</sup>O and a small amount of *N*-methyl-4-pyridone-*d*<sub>2</sub>.

**Registry No.**—2, 34236-36-7; 3, 15592-05-9; 4, 34268-13-8; 5, 34268-14-9; 6, 2701-45-3; sodium hydroxide, 1310-73-2; 4-methoxy-*N*-methylpyridinium iodide, 21823-37-0.

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