Pyridine derivatives and dichloromethane (DCM) are commonly used together in a variety of different applications. However, DCM slowly reacts with pyridine and a variety of other representative pyridine derivatives to form methylenebispyridinium dichloride compounds under ambient conditions. The proposed mechanism (two consecutive SN$_2$ reactions) was studied by evaluating the kinetics of the reaction between 4-(dimethylamino)pyridine and DCM. The second-order rate constants for the first ($k_1$) and second ($k_2$) substitutions were found to be 2.56(±0.06) × 10$^{-3}$ and 4.29(±0.01) × 10$^{-4}$ M$^{-1}$ s$^{-1}$, respectively. Because the second substitution is so much faster than the first, the monosubstitution product could not be isolated or detected during the reaction; it was synthesized independently in order to observe its kinetics.

### Scheme 1. Reaction of Pyridine with DCM

![Scheme 1](image)

While the literature reports that DCM reacts with primary, secondary, and tertiary aliphatic amines, the analogous reaction with pyridine derivatives under ambient conditions has not been reported. However, it was reported that DCM and pyridine formed compound 3a under increased temperature and pressure; the reaction was not observed at atmospheric pressure or room temperature, and an intermediate pyridinium adduct was never isolated. As might be expected, dibromomethane and diiodomethane show higher reactivity toward pyridine and its derivatives, and adducts from those have been reported. In addition, unsymmetrical bispyridinium derivatives have been synthesized by independently reacting a halomethyl pyridinium derivative with a dissimilar pyridine.

Since so little is known about the reaction of DCM with pyridines under ambient conditions we investigated a series of pyridine derivatives in order to determine the generality of the reaction and reactivity patterns. We also studied the kinetics of the reaction of DCM with 4-(dimethylamino)pyridine (DMAP) in order to elucidate the time course of the reaction, shed light on the reaction mechanism, and explain why the intermediate pyridinium adduct is not isolated or observed.

Thirteen different pyridine derivatives were dissolved in DCM and monitored for reaction with $^1$H NMR spectroscopy, looking for new downfield aromatic proton signals and the appearance of the distinctive methylene signal. The NMR samples were also inspected for the appearance of a

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The mechanisms for each step are simply assumed to be $S_N2$ displacements. More complex mechanisms involving deprotonation of acidic $C-H$ bonds appear to be ruled out by the lack of any detectable exchange of the methylene (or any) $C-H$ bonds when 2a, 2b, 3a, or 3b were allowed to stand in $D_2O$ solution for five days.

Given the favorable solubility of product 3b, we monitored the reaction kinetics of DCM with DMAP (1b) using a 0.7 M solution of DMAP in 1:1 (v/v) DCM/DMSO-$d_6$, monitored in quadruplicate for 31 days. Figure 1 shows three $^1H$ NMR spectra of the reaction mixture taken at the time points (in days) indicated on the right side of the spectra, with all the NMR signals assigned to specific protons on 1b or 3b. Several parts of the spectra were excited to conserve space so the DCM peak at 5.76 ppm is not shown (see the Supporting Information for the full spectra). On the basis of the spectra shown it is interesting to note the large downfield shift of all the protons in 3b due to the presence of the positive ring nitrogen, especially the methyl protons [(3b)ax], indicating significant charge transfer from the ring nitrogen to the $p$-dimethylamin moiety. Also notable is the lack of any signal from the intermediate (2b), which corroborates other reports and our own observation that the intermediate is not isolatable or observed during the course of the reaction.

On the basis of the $^1H$ NMR integrations and considering DCM (5 M) to be in excess, a pseudo-first-order rate law was used to obtain the second-order rate constant ($k_2$) for the overall reaction of $2.56(\pm0.06) \times 10^{-3} M^{-1} s^{-1}$ (for kinetic plots and calculations see the Supporting Information). Considering the lack of evidence for 2b, we made the assumption that the first step is rate determining ($k_1$) and that 2b is consumed by the second substitution immediately upon formation ($k_2$). On the basis of the steady-state approximation with $k_1\ll k_2$, then $k_2 \approx k_1$.

To monitor the kinetics of the second step, we synthesized 2b independently, starting with DMAP, thionyl chloride, and paraformaldehyde in acetonitrile as described by Anders et al.24 The kinetics of the second step were evaluated by using equimolar amounts of 0.126 M DMAP and 2b in DMSO-$d_6$, while monitoring the reaction in quadruplicate with $^1H$ NMR. Figure 2 shows three $^1H$ NMR spectra of the reaction mixture taken at the time points (in hours) indicated on the right side of the spectra, with all the NMR signals assigned to specific protons on 1b, 2b, or 3b. Most notable from this set of spectra is the time course of the reaction. Even at a much lower concentration, the second step of the reaction occurred in a matter of hours versus days and was readily monitored to higher completion (64% vs 50% based on NMR).

From the $^1H$ NMR integrations, $k_2$ was determined to be $4.29(\pm0.01) \times 10^{-4} M^{-1} s^{-1}$ when the disappearance of 1b was monitored ($k_{2(1b)}$) and $4.93(\pm0.04) \times 10^{-4} M^{-1} s^{-1}$ when the disappearance of 2b was monitored ($k_{2(2b)}$). The difference between these measured rates is likely due to a minor side reaction that was observed independently when 2b was

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**Table 1. Reactivity of Pyridine Derivatives toward DCM**

<table>
<thead>
<tr>
<th>pyridine derivative</th>
<th>reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-N(CH$_3$)$_2$ (1b)</td>
<td>yes</td>
</tr>
<tr>
<td>4-Bu (1c)</td>
<td>yes</td>
</tr>
<tr>
<td>4-NH$_2$ (1d)</td>
<td>yes</td>
</tr>
<tr>
<td>3-NH$_2$ (1e)</td>
<td>yes</td>
</tr>
<tr>
<td>4-‘(4-pyridyl) (1f)</td>
<td>yes</td>
</tr>
<tr>
<td>2-Cl</td>
<td>no</td>
</tr>
<tr>
<td>2-Cl</td>
<td>no</td>
</tr>
<tr>
<td>2-NH$_2$</td>
<td>no</td>
</tr>
<tr>
<td>2-CH$_3$</td>
<td>no</td>
</tr>
<tr>
<td>2-(CH$_3$)$_2$OH</td>
<td>no</td>
</tr>
<tr>
<td>2-(CH$_3$)$_2$SH</td>
<td>no*</td>
</tr>
</tbody>
</table>

*Thiols react with DCM.

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**Scheme 2. Proposed Mechanism for the Reaction of Pyridine Derivatives with DCM**

![Scheme 2](image-url)

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dissolved in DMSO-$d_6$ that had absorbed atmospheric moisture. Minor peaks at 8.4 and 7.1 ppm in the 4 and 8 h NMR spectra are due to this reaction and would explain why the rate constant when following the disappearance of $2b$ is slightly larger than that when following $1b$. This side reaction may be due to H$_2$O in the NMR solvent displacing a chloride ion from the methylene position (see the Supporting Information for the full NMR spectra of the kinetic run, proposed structure of side product, and proton assignments). Since there is ambiguity in $k_{2b}$, the lower rate $k_{21b}$ will be considered the rate of the second substitution $k_2$. On the basis of the ratio of the first and second step rate constants, the second substitution reaction is $\sim$17 000 times faster than the first step.

To estimate the amount of $2b$ present under steady state conditions, $k_1$ and $k_2$ were introduced into the steady state approximation and the steady-state concentration $[2b]$ was estimated to be $2.5 \times 10^{-4}$ M (for kinetic plots and calculations see the Supporting Information). On the basis of the rate enhancement for the second step and the low concentration of $2b$ at the steady state, the assumption that the second step is much faster than the first and that the initial substitution is rate determining was supported. The transient nature of $2b$ can be understood in terms of the electronic environment of the methylene group ($2b$)$_M$. With a pyridinium moiety and a chlorine atom attached, ($2b$)$_M$ is extremely electrophilic, making the intermediate much more reactive than DCM. In general, the substituent effect of a quaternary ammonium ion, such as a pyridinium group, is understood to be more electron withdrawing than a chlorine substituent,\textsuperscript{27}

and that should be expected to increase reactivity in a nucleophilic substitution. In fact, the pyridinium ion from DMAP is relatively electron-rich, drawing electron density from the dimethylamino group (as detected in NMR spectra). Thus other substituted pyridinium ions should show an even greater electron-withdrawing substituent effect, and these should show even greater reactivity in the second substitution reaction. Although intermediate 2a was successfully synthesized in a manner similar to 2b, the corresponding reaction could not be successfully monitored due to the insolubility of 3a. It appears that chloride displacement is more favorable than pyridine displacement:24 we find no evidence for reaction of 2b with its chloride counterion to regenerate 1b. We did not investigate whether one pyridine could displace another from an intermediate of structure 2.

On the basis of the information reported here, caution should be taken when using pyridines in DCM for organic syntheses, especially in the case of DMAP, which reacts fastest of the six derivatives studied and the product of which remains dissolved in DCM. When using pyridine derivatives as proton acceptors, 2- (or 2,6-) substituted pyridines should work well without the added concern about byproduct formation.26

**Experimental Section**

**Detection and Isolation of Disubstituted Products (3a–f).** To determine the reactivity of pyridine derivatives with DCM, a sample of the pyridine derivative in DCM (typically either a 2.1 mol ratio of pyridine derivative to DCM or the maximum concentration of pyridine derivative that was soluble in DCM) was diluted to twice its original volume with DMSO-d$_6$ capped, and sealed with Parafilm in an NMR tube. An NMR spectrum was taken immediately and every two weeks for 2 months to see if new peaks corresponding to the methylene bispyridinium compound were observed. The NMR tube was also monitored for the appearance of precipitate. In the case of a positive result from either observation, a larger solution of the pyridine derivative was isolated via vacuum filtration, rinsed with ice-cold DCM, and dried in vacuo at 60 °C overnight.

1.1'-Methylenebis(pyridinium) dichloride (3a): mp 253 °C dec; $^1$H NMR (400 MHz, D$_2$O) δ 8.11 (d, J = 7.4 Hz, 4H), 6.87 (d, J = 7.4 Hz, 4H), 6.22 (s, 2H), 3.18 (s, 12H); $^{13}$C NMR (101 MHz, D$_2$O) δ 157.0, 140.4, 108.2, 73.0, 39.8; ESI (+) HRMS calcd for M$^{2+}$ (C$_{11}$H$_{12}$N$_4$) 25% yield, mp 170 °C (lit. mp 172 °C); $^1$H NMR (400 MHz, D$_2$O) δ 9.05 (d, J = 6.2, 2H), 8.65 (t, 1H), 8.13 (t, 2H), 6.29 (s, 2H); $^{13}$C NMR (101 MHz, D$_2$O) δ 148.3, 144.7, 128.7, 64.7.

1-Chloromethyl-4-(dimethylamino)pyridinium chloride (2b): mp 25% yield, mp 265 °C dec; $^{1}$H NMR (400 MHz, DMSO-d$_6$) δ 8.56 (d, J = 7.4 Hz, 2H), 7.18 (d, J = 7.4 Hz, 2H), 6.32 (s, 2H), 3.26 (s, 6H); $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 156.4, 141.8, 108.3, 62.3.

**NMR Kinetics Experiments for the Overall Reaction of DCM with DMAP.** To each of four NMR tubes was added 0.6 mL of a 0.7 M solution of DMAP in 1:1 (v/v) DCM/DMSO-d$_6$. The tubes were capped and sealed with Parafilm, inverted 3 times, and analyzed with a 400 MHz NMR spectrometer. NMR spectra were recorded 11 times over the course of 31 days. The spectra were integrated in reference to the DMSO-d$_6$ solvent peak and the relative peak areas of the reactant and product peaks were used to determine the decrease in concentration of DMAP and subsequently the rate constant for the overall process.

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**Supporting Information Available:** General experimental details, compound characterizations ($^1$H NMR, $^{13}$C NMR, IR, UV–vis, and HRMS spectra), kinetic plots, and calculations. This material is available free of charge via the Internet at http://pubs.acs.org.