N-METHYLIMIDAZOLE CATALYZED ACETYLATION FOR THE ANALYSIS OF HYDROXY COMPOUNDS

BY

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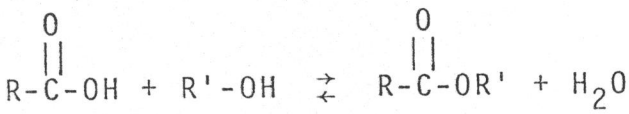
I. INTRODUCTION

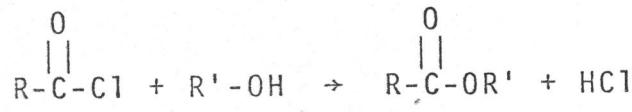
1. Analytical Acylation

Acylation is a convenient method for the quantitative determination of hydroxy groups, both phenolic and alcoholic, as well as amino groups. The use of an organic acid as the acylating agent is not feasible since the reaction is an equilibrium.

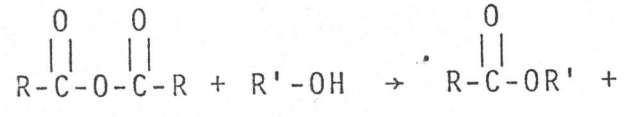


$$R\text{-}C(=O)\text{-}OH + R'\text{-}OH \rightleftarrows R\text{-}C(=O)\text{-}OR' + H_2O \qquad (1)$$

A quantitative reaction is thus not possible unless the water formed is either removed or otherwise consumed. Hence, quantitative acylation is accomplished with the acid chloride or the acid anhydride.



$$R\text{-}C(=O)\text{-}Cl + R'\text{-}OH \rightarrow R\text{-}C(=O)\text{-}OR' + HCl \qquad (2)$$



$$R\text{-}C(=O)\text{-}O\text{-}C(=O)\text{-}R + R'\text{-}OH \rightarrow R\text{-}C(=O)\text{-}OR' + RCOOH \qquad (3)$$

The amount of hydroxyl function in the sample may be determined by measuring the quantity of the acylating reagent consumed or the amount of one of the products formed. The

first approach is the one most frequently applied in titrimetric methods.

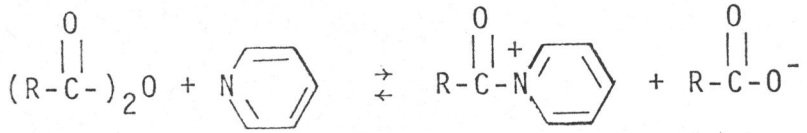
Carboxylic acid anhydrides are the most commonly used acylation reagents. The carboxylic halides are also used (1, 2) but are more reactive than the anhydrides and hence more difficult to handle. At present, three anhydrides are widely used for titrimetric hydroxyl group determinations - acetic anhydride (Ac_2O), phthalic anhydride, and pyromellitic dianhydride.

When the determination of hydroxy function depends on the measurement of the acylating agent consumed, the most common reagent is acetic anhydride (Ac_2O). The titrimetric finish requires the quantitative hydrolysis of unreacted anhydride to acid, which is then titrated with standard base.

2. Acylation Catalysts

Pyridine is the classical catalyst for analytical acylations of hydroxy groups with acid anhydrides (3-6). It serves as a catalyst and solvent for the reaction. In addition, pyridine is a weak enough base so that carboxylic acids can be titrated in the presence of pyridine by using a strong base such as sodium hydroxide. The acylation occurs via nucleophilic catalysis by the pyridine, with the formation of the acylpyridinium ion as the intermediate (7), as shown in Equations 4-5 for the acylation of an

alcohol.



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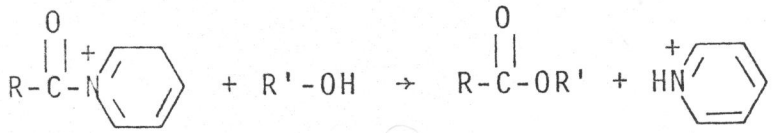


(5)

Pyridine thus serves as a proton acceptor as well as a catalyst, with the desirable result of displacing the equilibrium in favor of the product. Pyridine-catalyzed acylations are widely used in the titrimetric determinations of hydroxy and amino groups, as well as in derivatization procedures prior to spectrophotometric measurements and gas chromatographic separations (6, 27, 35).

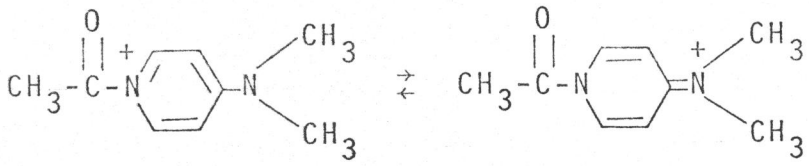
Despite the widespread use of pyridine as a catalyst in such acylations, it is not the ideal reagent for this purpose. The reactions are relatively slow, with reaction times of 0.5-2 hours at reflux temperatures being common (6). Another disadvantage is the noxious odor of pyridine, which may require the use of a fume hood during analysis.

Several other compounds have been studied as potential catalysts for acylations. Fritz and Schenk (8) reported two rapid perchloric acid-catalyzed acetylation methods for alcohols. They later extended these methods to the determination of phenols, thiols and amines (9). Schenk *et al*.

(10) studied various tertiary amines as catalysts for the acetylation of cyclohexanol with acetic anhydride, and found triethylenediamine to be about 50 times more effective than pyridine. This catalyst is also reported to be superior to pyridine in the acylation of alcohols with the acid chloride of the 2,4-dinitrophenylhyrazone of pyruvic acid (11). Imidazole has been extensively studied as a nucleophilic catalyst and has been reported to catalyze acylations by pyromellitic dianhydride (12).

Steglich and Höfle (13, 14) have reported that 4-dimethylaminopyridine (DMAP) is superior to pyridine as a catalyst for synthetic acylations. Connors and Albert (15) applied DMAP to the titrimetric determination of alcohols by acetylation with acetic anhydride. In this laboratory, we undertook a study to determine the effectiveness of DMAP as a catalyst for derivatization of alcohols prior to gas chromatographic separation. DMAP was found to be effective for this purpose. Subsequently, Rowe and Machkovech (16) reported a gas chromatographic method for the analysis of clindamycin palmitate hydrochloride using DMAP-catalyzed acetylation.

The superiority of DMAP over pyridine as an acylation catalyst is ascribed to the stabilization of the corresponding acylpyridinium ion (15).



For the acylation of isopropanol with Ac_2O, DMAP was shown to be about 2 x 10^4 times more effective than pyridine (15) as a catalyst. A DMAP-pyridine solution is now commercially available as part of the "Pyridine-Plus Acetylation Kit" for the derivatization of alcohols and amines (43).

In spite of its greater effectiveness, DMAP has not replaced pyridine as an analytical reagent. It is a solid and hence cannot serve as a solvent in these reactions. In addition, its catalytic activity is so great that side reactions occur, made evident through the rapid discoloration of the reaction medium. This discoloration affects the accuracy of the visual endpoint in titrimetric procedures, and limits the concentration of DMAP that can be used. Since the DMAP concentration in the reaction mixture has to be low, another base is necessary to serve as the proton scavenger. As a consequence, the analytical applications of DMAP thus far have simply incorporated DMAP into the usual pyridine/Ac_2O system. Thus, although the use of DMAP achieves a useful reduction in reaction time, the DMAP/pyridine/Ac_2O system is not an ideal one because of the prevalence of side reactions and the presence of pyridine.

3. Rationale for Study

It was felt that there was a need for a better catalyst for acylation reactions. The following properties were considered desirable for such a catalyst:

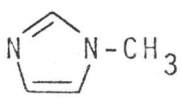
(a) It should be a nucleophilic catalyst with an effectiveness greater than pyridine;

(b) It should have a catalytic activity less than that of DMAP so that it can be used in high enough concentrations to serve as both the proton scavenger and catalyst;

(c) It should be a liquid for ease of use; and

(d) It should be a fairly weak base to prevent interference with titrimetric finishes.

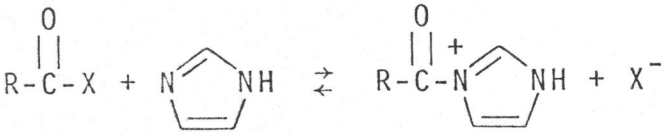
On the basis of arguments summarized below and some preliminary data (17), it was suggested that N-methylimidazole (1-methylimidazole) (NMIM) (I) may be this desirable catalyst. The theoretical basis of this conclusion follows.



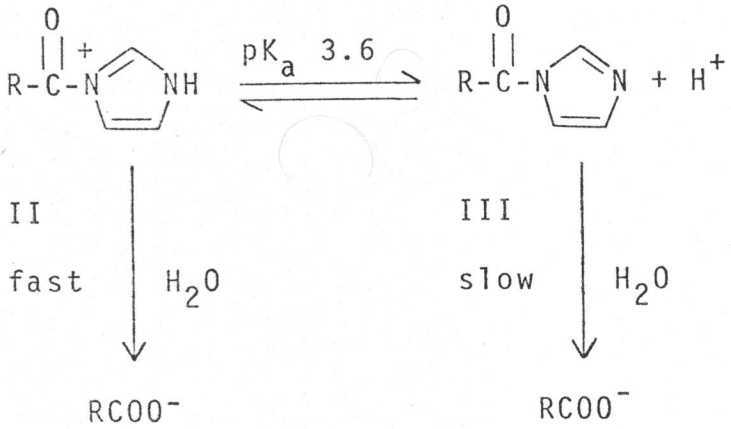
I

Imidazole-catalyzed acyl transfer reactions from reactive acyl compounds such as acid anhydrides and aromatic esters have been well studied (18-20). If RCOX represents such an activated acyl compound, the mechanism can be

summarized in Equations 6-7.



(6)



(7)

In this scheme water is shown as the nucleophile, but the mechanism is the same for other nucleophiles. The acylimidazolium ion (II) is much more reactive than the neutral acylimidazole (III) because its leaving group is the neutral imidazole molecule, which is the more stable form under mild conditions. The second-order rate constants for the hydrolysis at 25° of N-acetylimidazolium ion and of N-acetylimidazole are 5×10^{-2} M^{-1} min^{-1} and 9×10^{-5} M^{-1} min^{-1} respectively (21). In addition to catalyzing the acyl transfer reaction, imidazole also catalyzes the hydrolysis of N-acetylimidazole. This must be a general base catalysis, since nucleophilic attack by imidazole

would regenerate the substrate.

Since the acylimidazolium ion is the intermediate via which most of the catalysis occurs, it is reasonable to expect that NMIM will also be an effective catalyst, perhaps even better than imidazole, for acylation reactions. Jencks and Carriuolo (23) studied the catalysis of some acyl transfer reactions by imidazole and NMIM, and found similar rates for these two catalysts. They concluded that the formation of the acylimidazolium ion was rate determining in their system since,

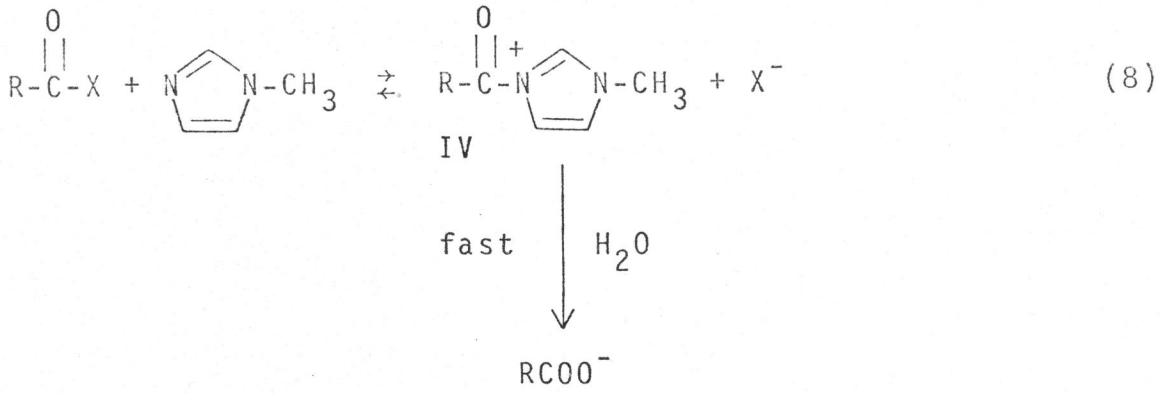
(a) imidazole and NMIM have similar pK_a's (the pK_a of imidazole is 6.95 and that of NMIM is 7.05 (20));

(b) the reaction rate was proportional to the concentration of the catalyst and not the acceptor;

(c) no accumulation of acylimidazole was observed; and

(d) the rates of the overall reactions were the same as the rates of reaction of the acyl donor with the catalyst in the absence of an acceptor.

The authors also predicted that if the attack of the nucleophile on the intermediate were rate-determining, then the NMIM-catalyzed reaction would be much faster than that with imidazole. This is because there is no possibility of deprotonation in the corresponding intermediate, the N-acyl-N' methylimidazolium ion (IV), as shown.



(8)

This species would therefore be expected to react with the acceptor much faster than an equilibrium mixture of acylimidazole and acylimidazolium ion. The N-acyl-N'-methylimidazolium ion is an excellent model for the reactions of the acylimidazolium ion, and has been used to show that imidazole catalysis proceeds via the formation of the acylimidazolium ion (21).

Table I compares published second-order rate constants and relative rates for the alkaline hydrolysis of acetylimidazole (AcIm), N-acetyl-N'-methylimidazolium ion ($AcNMIM^+$) and Ac_2O (21, 24). The same order of reactivity is seen with other nucleophiles. The reactivity of the acetylimidazolium ion ($AcHIm^+$) will be about equal to that of $AcNMIM^+$.

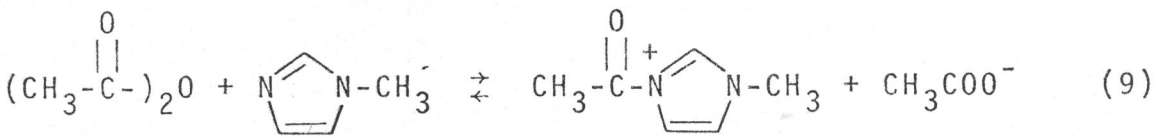
If Ac_2O is reacted with imidazole, rapid quantitative formation of the N-acetylimidazole occurs (24). The pK_a of imidazole is 6.95 (20) and that of N-acetylimidazole is 3.6 (23). Therefore a neutral or basic medium is needed to place the imidazole in its reactive conjugate base form.

Table I. Rates of Alkaline Hydrolysis of Some Activated Acetyl Compounds

Compound	k_{OH} (M^{-1} min^{-1})	Relative Rate	Reference
AcIm	1.9×10^4	(1.0)	24
Ac_2O	5.8×10^4	3	24
$AcNMIM^+$	9.0×10^6	470	21

In this medium, however, the N-acetylimidazole will exist almost entirely as the neutral, relatively unreactive species. Thus the net result is that the more reactive Ac_2O (refer to Table I) is transformed to the less reactive AcIm. From the point of view of the overall transfer of an acetyl group from Ac_2O to a hydroxy compound, the presence of imidazole is predicted to inhibit the reaction rate.

The pK_a of NMIM is 7.05 (20). Thus, on reaction with Ac_2O, $AcNMIM^+$ is formed; this intermediate is more reactive than Ac_2O (refer to Table I). Thus, NMIM is predicted to catalyze acylations by Ac_2O. The mechanism for acetylation of alcohols in a NMIM/Ac_2O system is probably as shown in Equations 9-10.



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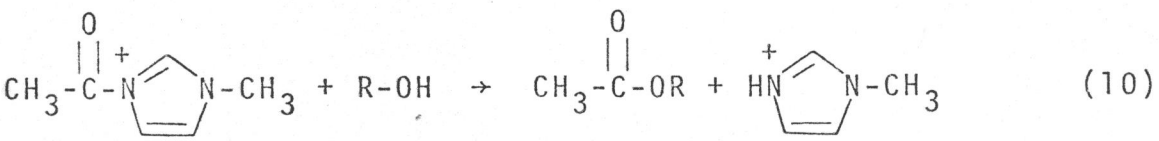

(10)

In comparing the relative effectiveness of pyridine and NMIM as nucleophilic acylation catalysts, pyridine might be thought to be superior, since the acetylpyridinium ion is much more reactive than $AcNMIM^+$ (7). However, the formation of the acetylpyridinium ion is not favored, and is the rate-determining step in the Ac_2O/pyridine system,

while the nucleophilic attack of the substrate on $AcNMIM^+$ is rate-determining in the Ac_2O/NMIM system. Hence, NMIM is predicted to be superior to pyridine as a catalyst for acylations.

Some preliminary studies showed that NMIM did indeed catalyze acetylation of alcohols and was superior to pyridine as a catalyst; in addition, imidazole was observed to inhibit this reaction (25). Based on these results, it was felt that NMIM warranted further investigation as an analytical acylation catalyst. This study was undertaken to establish NMIM as an effective catalyst for the analytical acetylation of hydroxy compounds with Ac_2O, and to compare its catalytic activity with those of pyridine and DMAP.

II. EXPERIMENTAL

1. Materials

All the hydroxy compounds used were analytical reagent grade and were used directly. n-Propanol, isopropanol, iso-butanol and phenol were obtained from Mallinckrodt Chemical Company. sec-Butanol and 1,2-propanediol were obtained from Aldrich Chemical Company. n-Butanol, n-amyl alcohol and tert-butanol were Baker Analyzed. Ethylene glycol was obtained from Matheson, Coleman and Bell. The purities of these compounds were checked by gas chromatography on a Tracor 550 gas chromatograph equipped with a flame-ionization detector, and using a temperature program. The conditions were as follows: Column: 5% Carbowax 20 M on Chromasorb W, AW, DMCS treated (both obtained from Tracor Analytical Instruments Division). Initial Temp: 50°. Program Rate: 10°/min. Each of the hydroxy compounds showed only one peak, and no unexpected peaks were observed.

Pyridine (ACS certified) was obtained from Fisher Scientific Company. Imidazole and N-methylimidazole (both from Aldrich Chemical Company) were used directly. DMAP (Aldrich Chemical Company) was recrystallized from Skellysolve^{R} B; MP 113° [lit. 114° (36)].

Acetic anhydride (Ac_2O) was analytical grade (Mallinkrodt Chemical Company). Sodium hydroxide pellets

(ACS) were obtained from Mallinkrodt, and thymolphthalein was obtained from Eastman Organic Company. N,N-dimethylformamide (DMF) was reagent grade (Aldrich Chemical Company) and was used directly.

All water used was deionized distilled water.

0.5 N sodium hydroxide was prepared by diluting 30 ml of saturated sodium hydroxide solution to 1 liter with freshly boiled water. The solution was standardized against potassium hydrogen phthalate using 2 drops 1% phenolphthalein as indicator.

1% phenolphthalein solution was prepared by dissolving 0.5 g phenolphthalein in 50 ml absolute ethanol. 0.2% thymolphthalein solution was prepared by dissolving 0.1 g in 50 ml absolute ethanol.

The Ac_2O reagent solution was prepared by diluting 15 ml of Ac_2O to 100 ml with DMF.

2. Apparatus

The reaction temperature was maintained at 45 $\pm$ 0.1° using a thermostatic bath with a heater and circulator (E. H. Sargent and Company).

Potentiometric titrations were carried out with an Orion Model 801 pH meter* using a Sargent Welch combination electrode #S100070.

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*The Orion pH meter was graciously loaned by Professor J. R. Robinson.

3. Kinetic Measurements

NMIM, DMF, and solutions of Ac_2O and of a hydroxy compound in DMF were equilibrated at 45°. The concentrations of these solutions were known. Appropriate volumes of NMIM, the Ac_2O solution, and the sample solution were added to a 125-ml glass-stoppered conical flask and were well-mixed. The flasks were maintained at 45°. At known times, 5.0 ml samples of the reaction mixture were withdrawn, discharged into 20 ml of water and allowed to cool to room temperature. If the mixture was not homogeneous, 20 ml of absolute ethanol was added. The solutions were then titrated with standard 0.5 N sodium hydroxide solution using four drops of 0.2% thymolphthalein as indicator. Similar studies were carried out using pyridine and DMAP as catalysts at various concentrations.

4. Analytical Procedure

4.0 ml of a DMF solution containing two to three milliequivalents of a hydroxy compound was pipeted into a 125-ml glass-stoppered conical flask. Four ml of NMIM, followed by 4.0 ml of the Ac_2O reagent solution, was added, and the solution was well-mixed. The flask was maintained at 45° for seven minutes. After this time, 20 ml of distilled water was added to the flask, and the contents allowed to cool to room temperature. If the mixture was not homogeneous, 20 ml of absolute ethanol was added. Four drops of a

0.2% thymolphthalein solution in absolute ethanol were added and the solution was titrated with standard 0.5 N sodium hydroxide to a blue color. A blank determination was carried out, replacing the sample with 4.0 ml of DMF, and maintaining at 45° for three instead of seven minutes, to minimize discoloration.

The milliequivalents of the hydroxy compound contained in the sample taken for assay is given by $N(V_b - V_s)$, where V_b and V_s are the volumes (in ml) of sodium hydroxide of normality N required to titrate the blank and the sample, respectively.

5. Potentiometric Titrations

Potentiometric titrations were carried out to determine the pH at the end point of the titration and to compare the relative suitability of phenolphthalein and thymolphthalein as indicators.

About 2 milliequivalents of isopropanol contained in 4 ml of DMF was added to a glass-stoppered conical flask, followed by 1 ml of NMIM and 4 ml of a solution of Ac_2O in DMF. The reaction mixture was maintained at 45° for 20 minutes. After the reaction was complete, 20 ml of water was added and the contents allowed to cool to room temperature. A blank determination was carried out, replacing the sample with 4 ml of DMF. Four drops of 1% phenolphthalein were added and potentiometric titrations carried out on the

sample and the blank. The pH and color changes were followed simultaneously. A similar experiment was done replacing the phenolphthalein with 0.2% thymolphthalein. The pH meter was previously calibrated using a pH 9.18 borax buffer.

III. RESULTS

1. Potentiometric Titration Curves

Figure 1 shows the potentiometric titration curves for the blank and sample for the titration of these solutions with 0.5 N sodium hydroxide. The visual end point observed with phenolphthalein as indicator occurred at pH 9.8, and that with thymolphthalein at pH 10.75. Since the thymolphthalein end point was very near the potentiometric end point of the titration, and since it was sharper than the phenolphthalein end point, thymolphthalein is the indicator of choice.

2. Rate Studies of the NMIM-Catalyzed Acetylation of Isopropanol

The acetylation of isopropanol with Ac_2O using NMIM as catalyst was studied at various concentrations of NMIM and Ac_2O. Table II gives the results of these rate studies, expressed as the percent reacted as a function of time. Plots of percent reacted versus time under three different sets of conditions are shown in Figure 2. All reactions were carried out at 45°.

The rate of acetylation is expected to be described by Equation 11

Figure 1. Potentiometric titration curves of blank and sample solutions with 0.5335 N NaOH. Key: ○, blank; ●, sample.

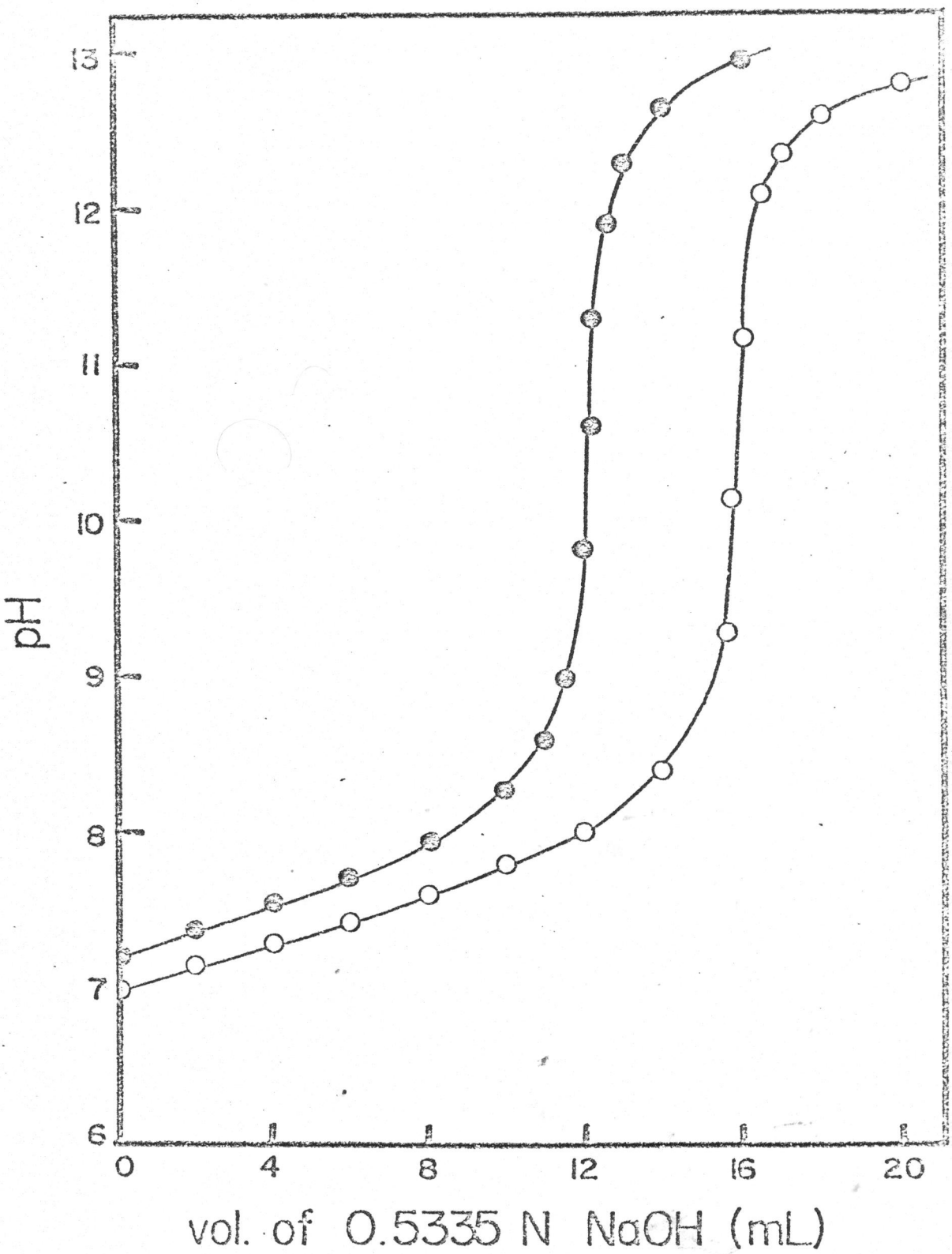

pH
13
12
11
10
9
8
7
6
0
4
8
12
16
20
vol. of 0.5335 N NaOH (mL)

Table II. Acetylation of Isopropanol in the Presence of Varying Initial Concentrations of Ac_2O and NMIM at 45°[a]

C^0_{NMIM} = 4.7 M, $C^0_{Ac_2O}$ = 0.8 M		C^0_{NMIM} = 1.4 M, $C^0_{Ac_2O}$ = 0.88 M	
t (min)	% reacted	t (min)	% reacted
1.0	60.0	0.8	19.0
1.7	85.5	2.5	62.0
3.0	95.4	5.0	84.4
4.8	100.0	8.3	94.0
7.0	100.0	10.5	97.0
		15.0	100.0
		20.0	100.0

C^0_{NMIM} = 2.5 M, $C^0_{Ac_2O}$ = 0.53 M		C^0_{NMIM} = 2.5 M, $A^0_{Ac_2O}$ = 0.8 M	
t (min)	% reacted	t (min)	% reacted
0.6	30.0	0.7	33.0
3.5	76.0	2.4	77.0
5.0	87.0	5.0	92.0
7.0	91.0	8.0	97.5
9.0	93.9	10.0	100.0
12.0	97.2	12.0	100.0
15.0	100.0		
20.0	100.0		

[a] Initial concentration of isopropanol was 0.4 M.

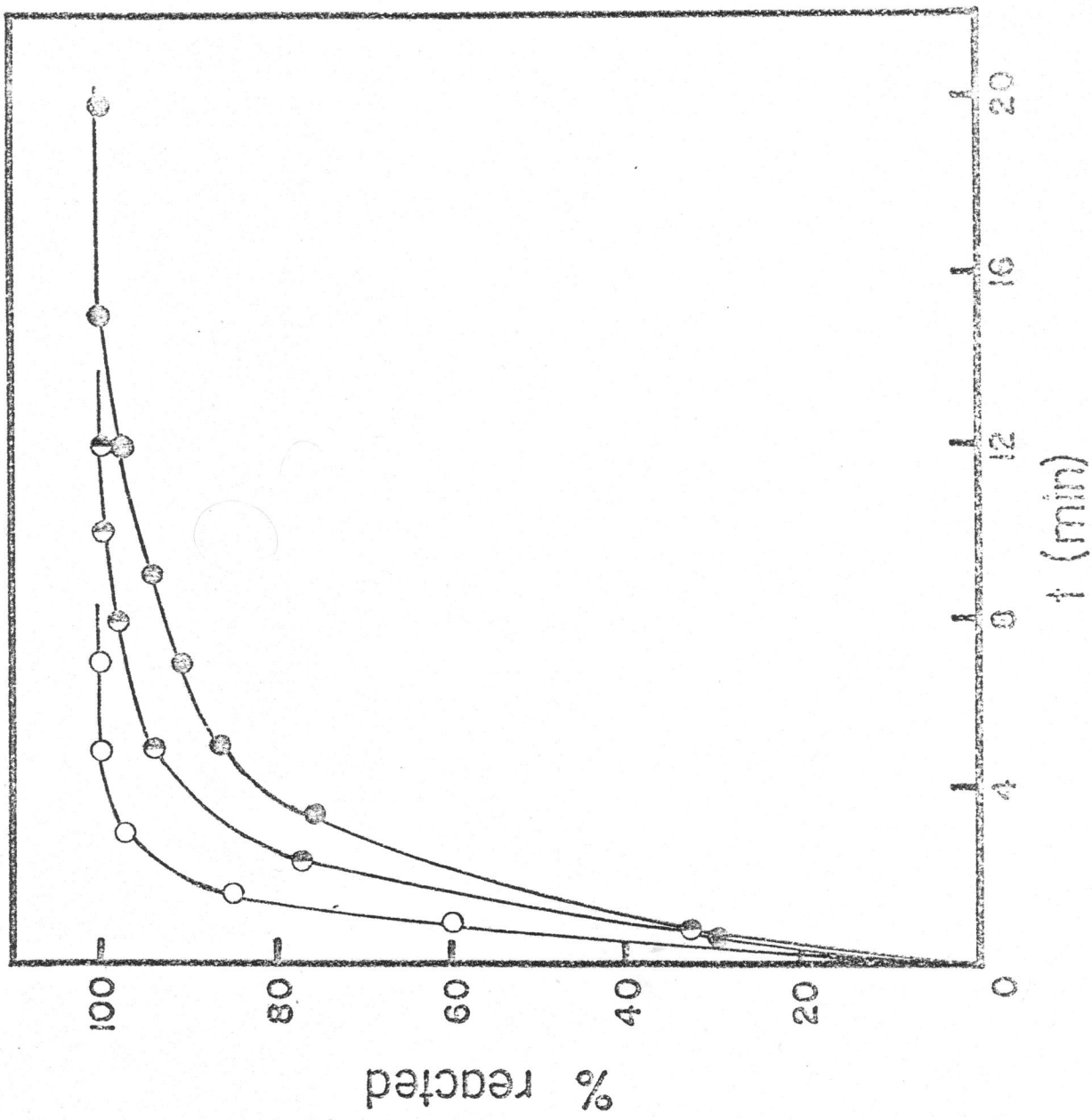


Figure 2. Time courses for acetylation of isopropanol by Ac_2O at 45°C and varying concentrations of NMIM and Ac_2O. Key: ○, 4.7 M NMIM and 0.88 M Ac_2O; ◑, 2.5 M NMIM and 0.88 M Ac_2O; and ●, 2.5 M NMIM and 0.53 M Ac_2O. Data from Table II.

$$V = k_{NMIM}[NMIM][ROH][Ac_2O] \quad (11)$$

where k_{NMIM} is a third-order rate constant. At constant catalyst concentration, this reduces to Equation 12

$$V = k'_{NMIM}[ROH][Ac_2O] \quad (12)$$

where $k'_{NMIM} = k_{NMIM}[NMIM]$; k'_{NMIM} is an apparent second-order rate constant.

If A represents a hydroxy compound and B represents Ac_2O, the integrated second-order rate equation can be written,

$$\log \frac{C_B}{C_A} = \log \frac{C_B^0}{C_A^0} + \frac{(C_B^0 - C_a^0)k't}{2.303} \quad (13)$$

C_A^0 and C_B^0 are initial concentrations; C_A and C_B are the concentrations at time t. The latter two quantities can be obtained from the relations

$$C_A = C_A^0 - N(V_b - V_s) \quad (14)$$

$$C_B = C_B^0 - N(V_b - V_s) \quad (15)$$

where,

N = normality of sodium hydroxide

V_b = volume of NaOH consumed by the blank, and

V_s = volume of NaOH consumed by the sample.

Therefore, $N(V_b - V_s)$ represents the amount of hydroxy compound reacted.

A plot of log C_B/C_A versus t will be a straight line if the reaction follows apparent second-order kinetics at constant catalyst concentration. The slope of this line will be $k'(C_B^0 - C_A^0)/2.303$, from which the second-order rate constant, k', at a given catalyst concentration can be determined. The third-order rate constant, k, is obtained from this on dividing by the concentration of the catalyst.

Figure 3 shows the second-order plot for the acetylation of isopropanol with Ac_2O using NMIM as the catalyst. The initial concentrations were [NMIM] = 1.4 M, C_A^0 = 0.46 M, and C_B^0 = 0.88 M. The reaction followed second-order kinetics up to 97 percent of reaction. The blank value for log C_B/C_A may not fall on the line due to the uncertainty in determining the exact time when the reaction is initiated.

Table III lists the apparent second-order and the third-order rate constants obtained for the acetylation of isopropanol at various concentrations of NMIM and Ac_2O. The mean third-order rate constant for this reaction was calculated to be 7.6×10^{-3} M^{-2} sec^{-1}, with a standard deviation of 0.3×10^{-3} M^{-2} sec^{-1}.

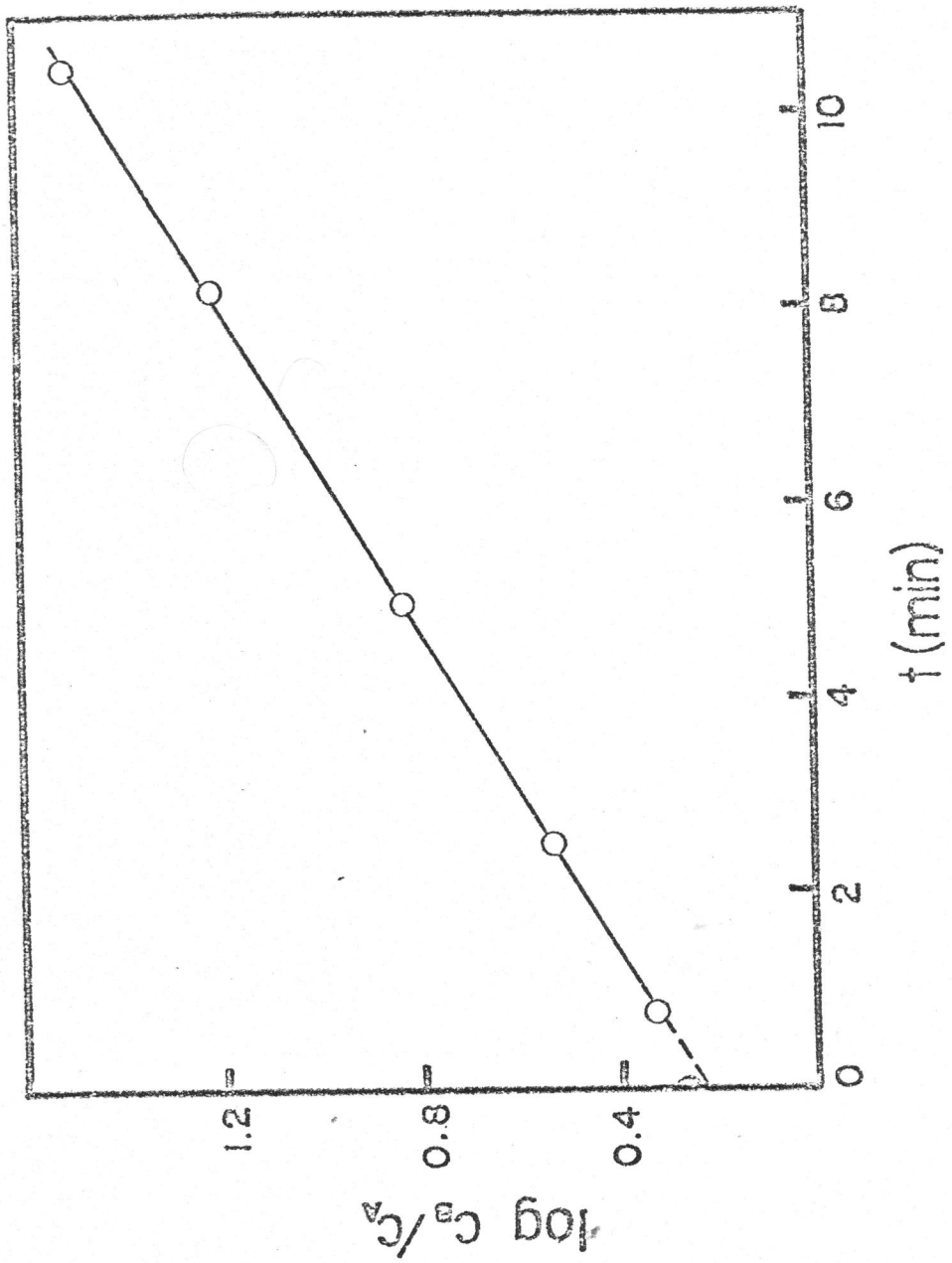


Figure 3. Second-order plot for the NMIM-catalyzed acetylation of isopropanol by acetic anhydride at 45°C.

Table III. Apparent Second-order Rate Constants and Third-order Rate Constants for the Acetylation of Isopropanol at 45° and at Various Concentrations of NMIM and Ac_2O

C_{NMIM}	C_{Ac_2O}	k' (M^{-1} sec^{-1})	k (M^{-2} sec^{-1})
2.5	0.80	1.9×10^{-2}	7.6×10^{-3}
2.5	0.53	2.0×10^{-2}	8.0×10^{-3}
1.4	0.88	1.0×10^{-2}	7.3×10^{-3}
4.7	0.80	3.4×10^{-2}	7.3×10^{-3}

3. Rate Studies of the NMIM-Catalyzed Acetylation of Some Other Hydroxy Compounds

Rate studies of the NMIM-catalyzed acetylation by Ac_2O were carried out for a variety of hydroxy compounds. Tables IV and V list the results of the rate studies for phenol - an aromatic hydroxy compound - and n-butanol - a primary alcohol - respectively. The data in these tables are plotted in Figure 4, along with data from Table II for isopropanol - a secondary alcohol - for the purpose of comparison. The rates of acetylation are in the order phenol > primary alcohol > secondary alcohol.

Second-order kinetic plots, similar to the ones for isopropanol, were made for all the hydroxy compounds studied. Figures 5 and 6 show the second-order plots for phenol and n-butanol.

It was observed that during the titration of the phenol sample solution with sodium hydroxide, the end point color faded very quickly, and therefore the titration had to be performed rapidly. This indicates that the phenyl acetate undergoes rapid hydrolysis in the presence of sodium hydroxide.

The attempted determination of tert-butanol, under the same conditions as for the other hydroxy compounds, yielded 36 percent acetylation in a 40-min reaction time. The data are shown in Table VI. From these data, a second-order plot was made as before, and the third-order rate constant

Table IV. NMIM-Catalyzed Acetylation of Phenol at 45°[a]

t (min)	% Reacted
1.0	85.9
2.0	91.0
3.0	95.0
4.0	97.3
5.0	100.0
7.0	100.0

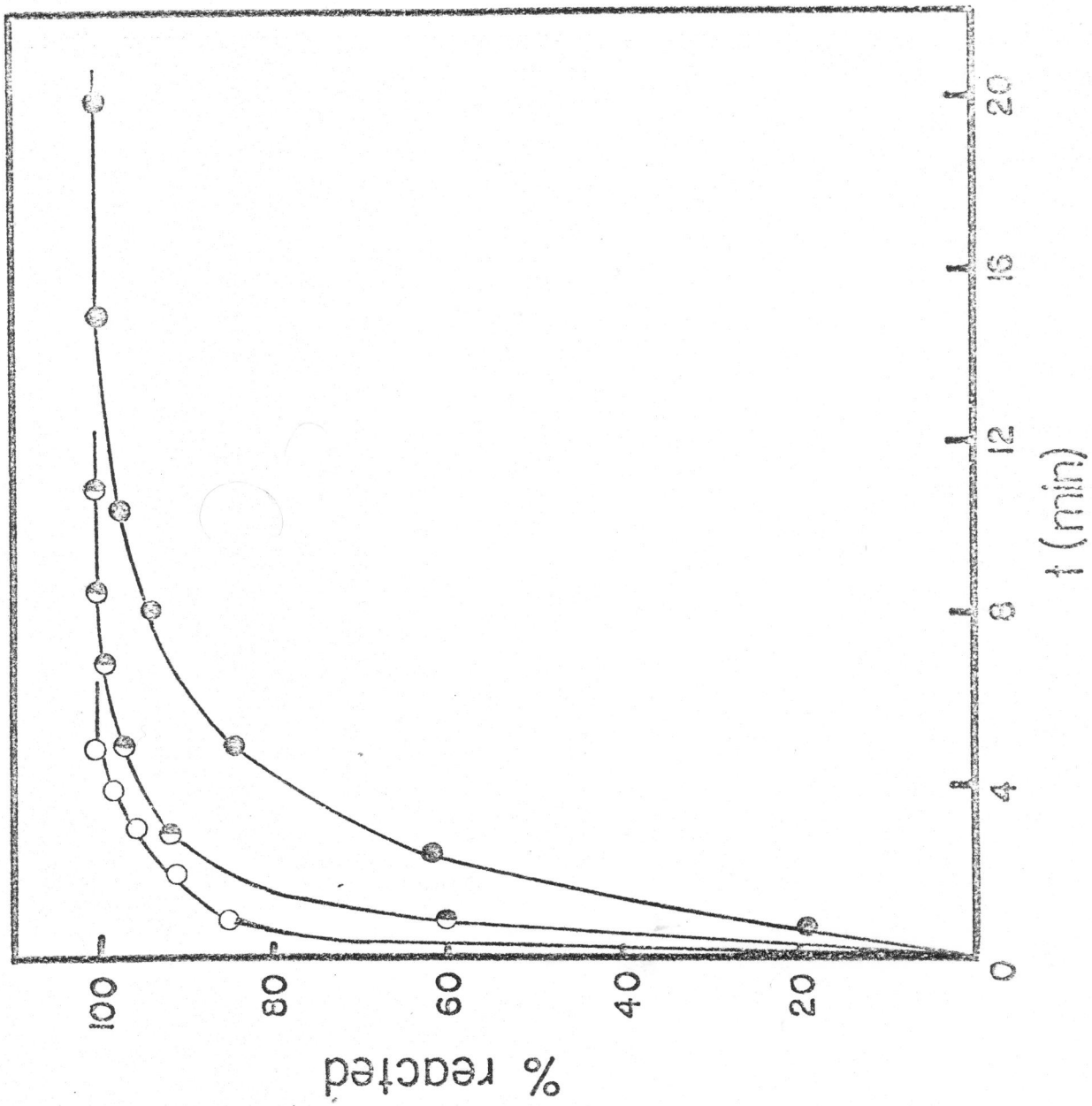
[a] $C^0_{NMIM} = 0.35$ M
$C^0_{Ac_2O} = 0.88$ M
$C^0_{Ph\text{-}OH} = 0.60$ M

Table V. NMIM-Catalyzed Acetylation of n-Butanol at 45°[a]

t (min)	% Reacted
1.0	76.3
2.0	90.0
3.0	95.8
4.0	97.9
6.0	100.0
8.0	100.0

[a] $C^0_{NMIM} = 0.88$ M
$C^0_{Ac_2O} = 0.88$ M
$C^0_{n\text{-}BuOH} = 0.38$ M

Figure 4. Time courses for the NMIM-catalyzed acetylation of phenol, n-butanol, and isopropanol at 45°. Key: ○, phenol acetylation catalyzed with 0.35 M NMIM; ◑, n-butanol acetylation with 0.88 M NMIM; ●, isopropanol acetylation with 1.41 M NMIM.


% reacted
100
80
60
40
20
0
4
8
12
16
20
t (min)

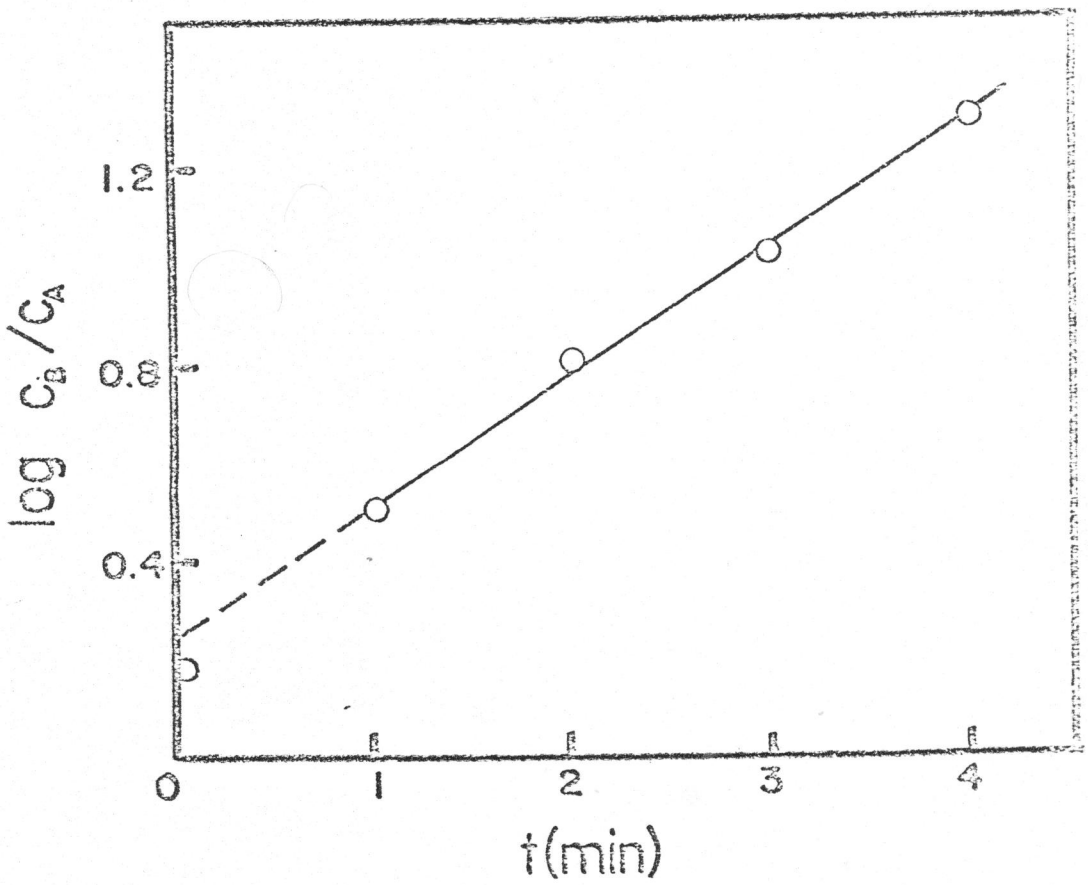


Figure 5. Second-order plot for the NMIM-catalyzed acetylation of phenol.

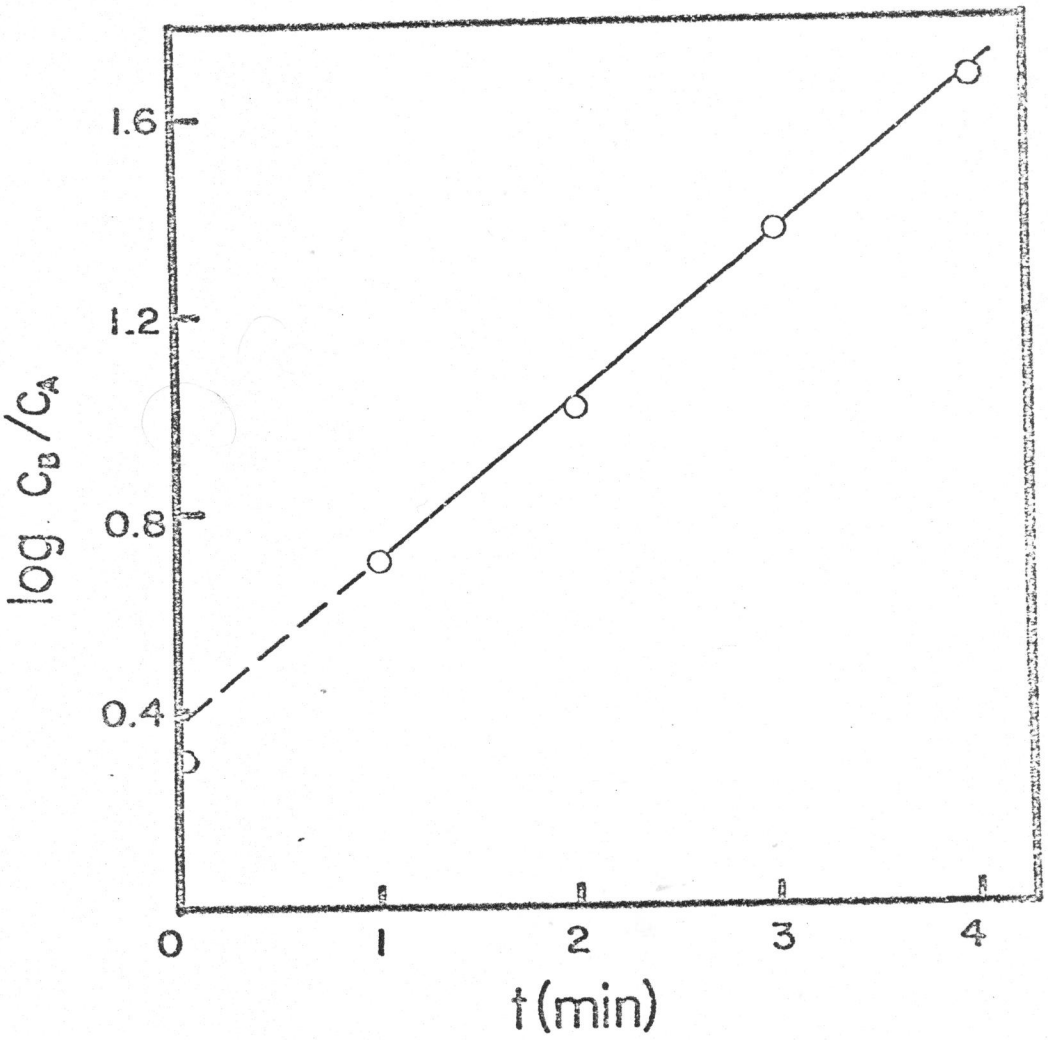


Figure 6. Second-order plot for the NMIM-catalyzed acetylation of n-butanol.

Table VI. NMIM-Catalyzed Acetylation of *tert*-Butanol at 45°[a]

t (min)	% Reacted
10.0	11.2
20.0	22.5
25.0	28.3
30.0	32.0
35.0	33.7
40.0	35.8

[a] $C^0_{NMIM} = 4.7$ M
$C^0_{Ac_2O} = 0.8$ M

estimated.

Table VII lists the third-order rate constants for the hydroxy compounds studies, for the reaction at 45°.

4. Comparison of NMIM and Pyridine as Acetylation Catalysts

The time course for the acetylation of isopropanol was followed using pyridine instead of NMIM as the catalyst. The reaction conditions were similar to those for the corresponding NMIM-catalyzed reaction. Table VIII shows the rate data for this study. Figure 7 shows the comparative time courses for the reactions with NMIM and pyridine as catalysts.

The reaction rate with pyridine as catalyst is expected to be given by the equation

$$V = k_{PYR}\,[PYR][ROH][Ac_2O] \qquad (16)$$

which can be simplified to

$$V = k'_{PYR}[ROH][Ac_2O] \qquad (17)$$

where $k'_{PYR} = k_{PYR}[PYR]$.

Figure 8 shows the second-order plot for the reaction. From this, the third-order rate constant, k_{PYR}, was estimated to be 2.1×10^{-5} M^{-2} sec^{-1}. The rate constant for

Table VII. Third-order Rate Constants for the NMIM-catalyzed Acetylation of Some Hydroxy Compounds at 45°[a]

Hydroxy Compound	$k \times 10^2/M^{-2}\ sec^{-1}$
Phenol	11.10
n-Propanol	4.80
n-Butanol	4.00
iso-Butanol	3.90
n-Amyl Alcohol	3.64
Isopropanol	0.76
sec-Butanol	0.35
tert-Butanol	0.0012

Table VIII. Pyridine-Catalyzed Acetylation of Isopropanol at 45°[a]

t (min)	% Reacted
5.0	0.0
10.0	4.0
15.0	6.4
20.0	7.6
25.0	9.9
30.0	12.9
60.0	21.6

[a] $C^0_{PYR} = 4.4$ M
$C^0_{Ac_2O} = 0.8$ M
$C^0_{iso\text{-}Pr\text{-}OH} = 0.34$ M

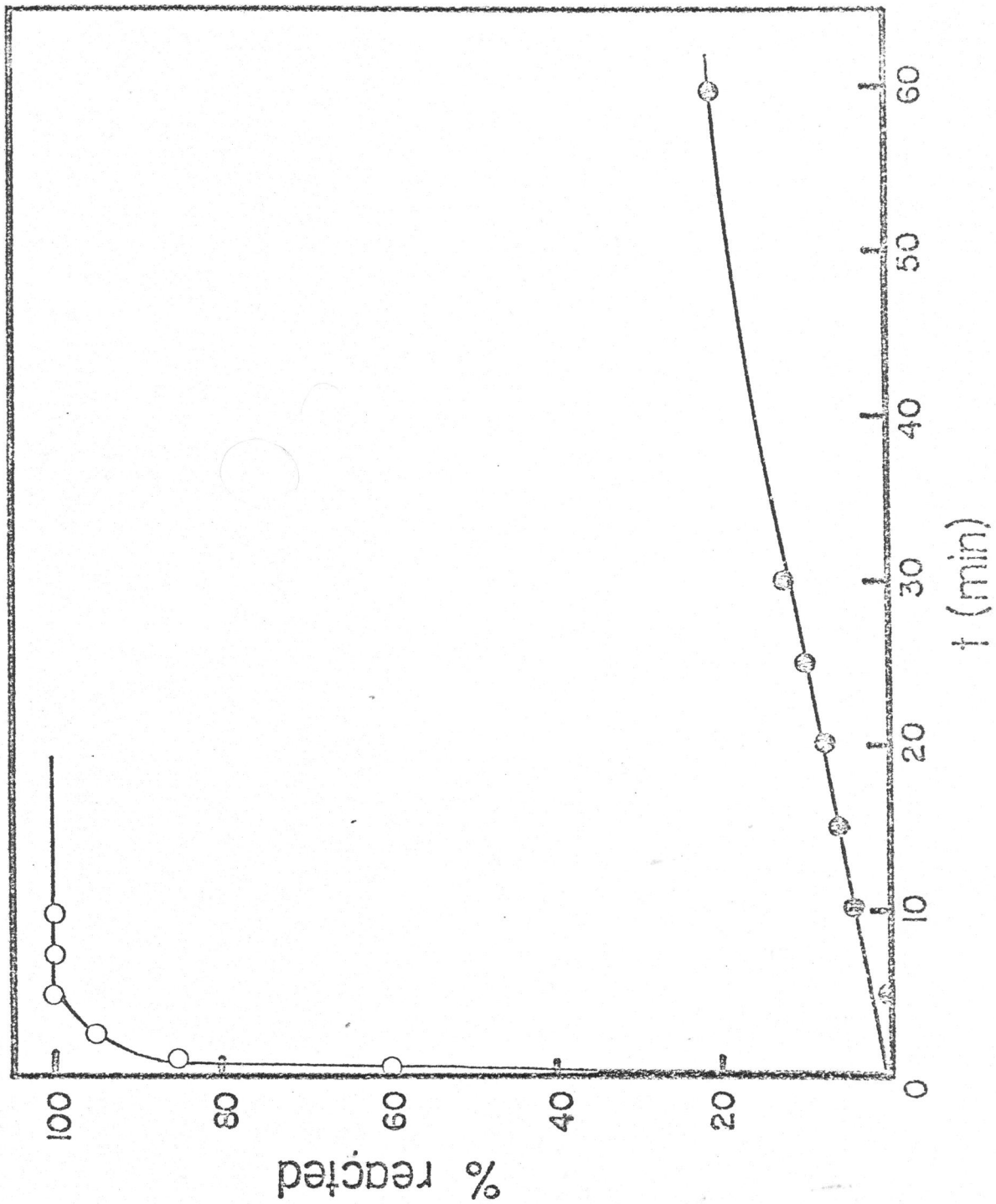


Figure 7. Time courses for the acetylation of isopropanol by 0.8 M Ac_2O at 45°. Key: ○, 4.7 M NMIM as catalyst; ●, 4.4 M pyridine as catalyst.

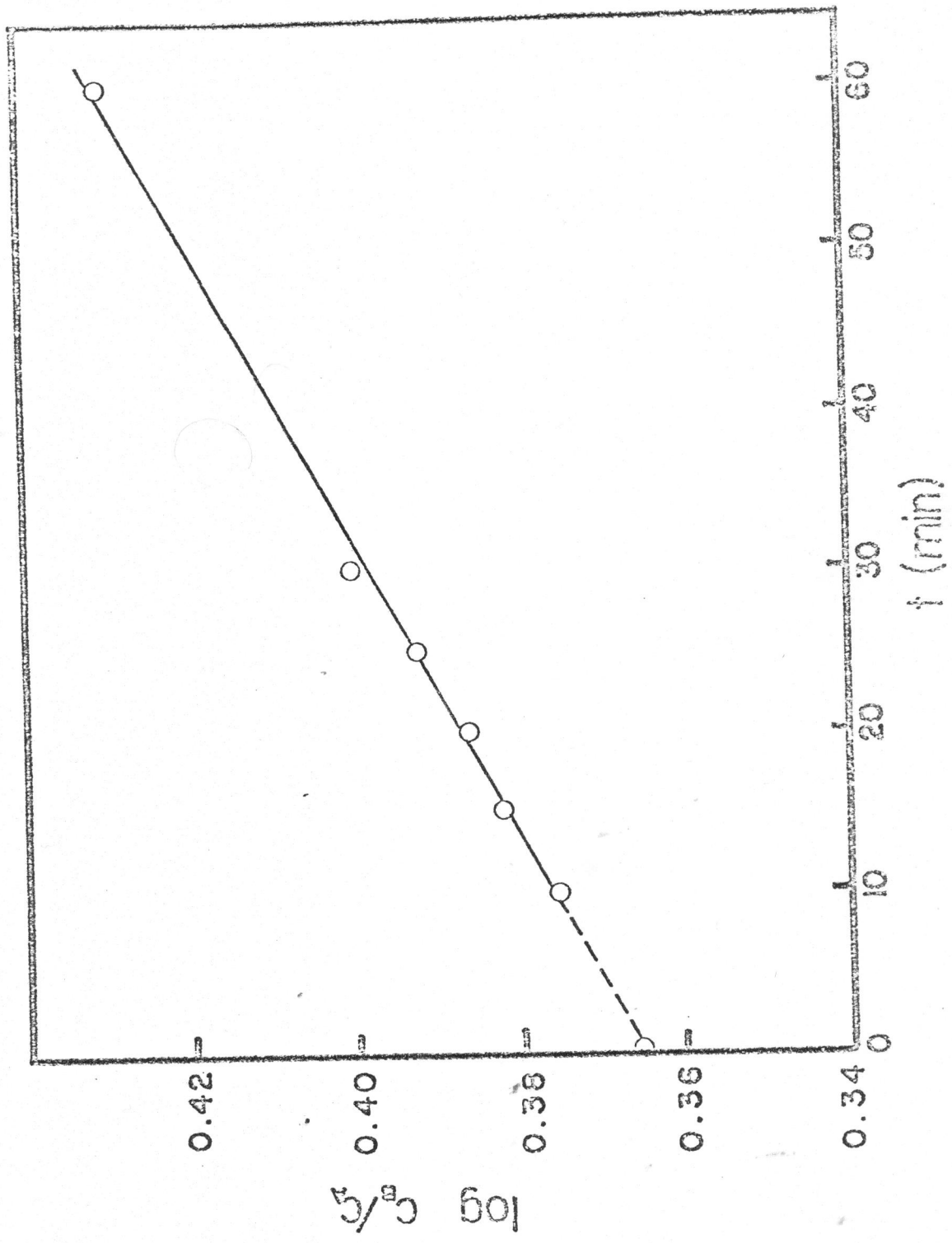


Figure 8. Second-order plot for the pyridine-catalyzed acetylation of isopropanol.

the reaction with NMIM is 7.6×10^{-3} M^{-2} sec^{-1} (Table VII). Therefore, NMIM is about 4×10^{2} times more effective as a catalyst than is pyridine in this reaction.

5. Comparison of NMIM and DMAP as Acetylation Catalysts

The time course for the acetylation of isopropanol with Ac_2O was followed using DMAP instead of NMIM as the catalyst. Studies were carried out using DMAP in the presence and absence of pyridine, since previous reports stated that pyridine was necessary to act as a proton scavenger. Table IX lists the rate data for studies under three different sets of conditions, and the data are plotted in Figure 9. The reaction goes to completion even in the absence of pyridine.

As before, the rate of reaction with DMAP as catalyst (in the absence of pyridine), is given by

$$V = k_{DMAP}[DMAP][ROH][Ac_2O] \tag{18}$$

$$V = k'_{DMAP}[ROH][Ac_2O] \tag{19}$$

where $k'_{DMAP} = k_{DMAP}[DMAP]$. Figure 10 shows the second-order plot for some of the data in Table IX. From this plot, the third-order rate constant, k_{DMAP}, was estimated to be 0.32 M^{-2} sec^{-1}.

Table IX. DMAP-Catalyzed Acetylation of Isopropanol at 45° in the Presence of Varying Concentrations of Pyridine and DMAP

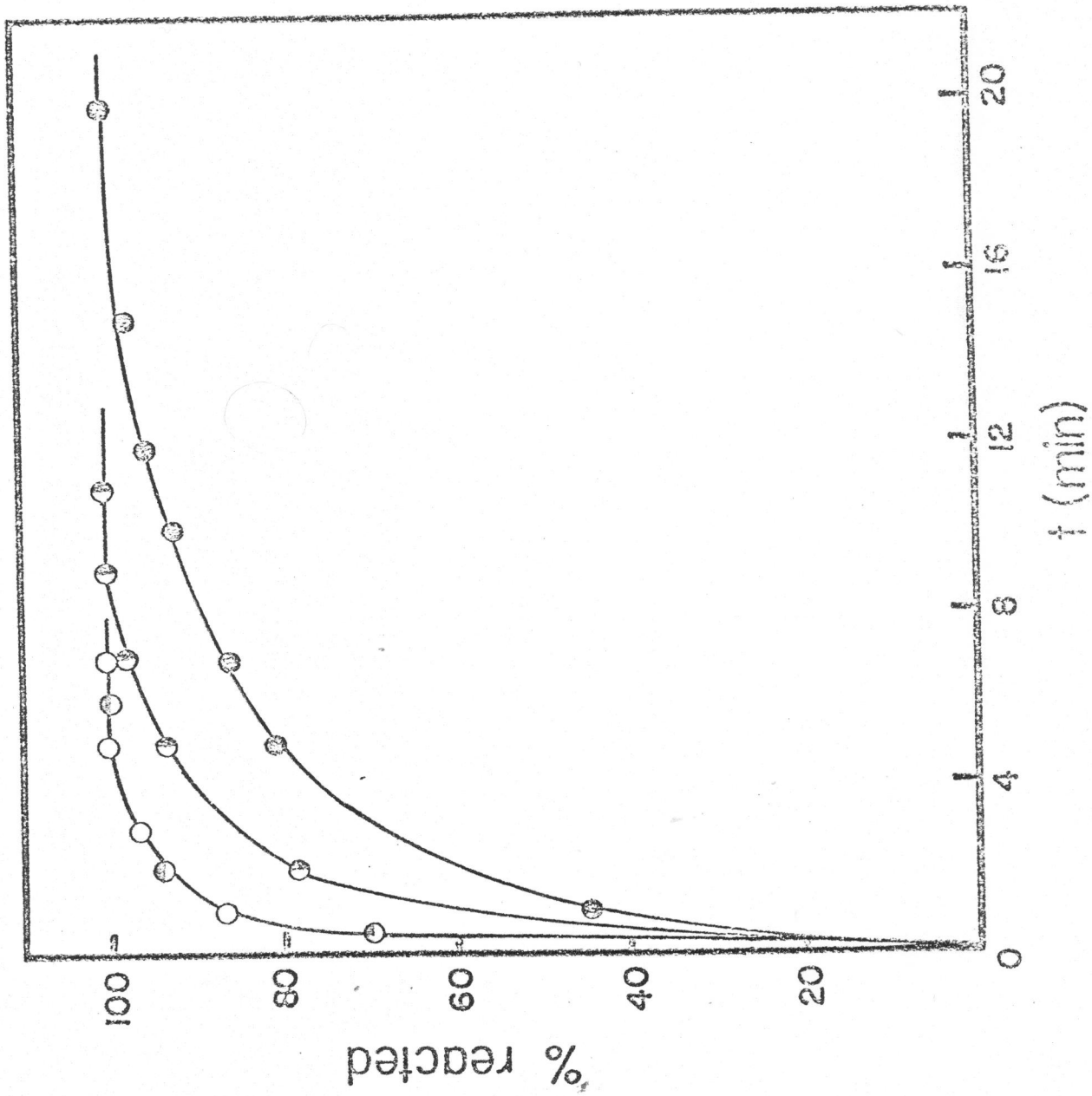
C^0_{DMAP} = 0.1 M, C^0_{PYR} = 4.4 M	
t (min)	% reacted
1.0	87.2
3.0	97.7
5.0	99.5
7.0	99.5

C^0_{DMAP} = 0.04 M, C^0_{PYR} = 4.4 M	
t (min)	% reacted
2.0	78.5
5.0	94.2
7.0	98.0
9.0	99.5
11.0	99.5

C^0_{DMAP} = 0.1 M	
t (min)	% reacted
0.5	70.0
2.0	94.2
5.0	99.5
7.0	99.5

C^0_{DMAP} = 0.036 M	
t (min)	% reacted
1.0	44.5
5.0	81.2
7.0	86.5
10.0	92.1
12.0	94,8
15.0	95.9
20.0	99.6

Figure 9. Time courses for the DMAP-catalyzed acetylation of isopropanol by Ac_2O at 45°C in the presence and absence of pyridine. Key: ○, 0.1 M DMAP, 4.4 M pyridine, 0.8 M Ac_2O; ◓, 0.1 M DMAP, 0.8 M Ac_2O; ◑, 0.04 M DMAP, 4.4 M pyridine, 0.8 M Ac_2O; and ●, 0.036 M DMAP, 0.7 M Ac_2O.


% reacted
100
80
60
40
20
0
4
8
12
16
20
t (min)

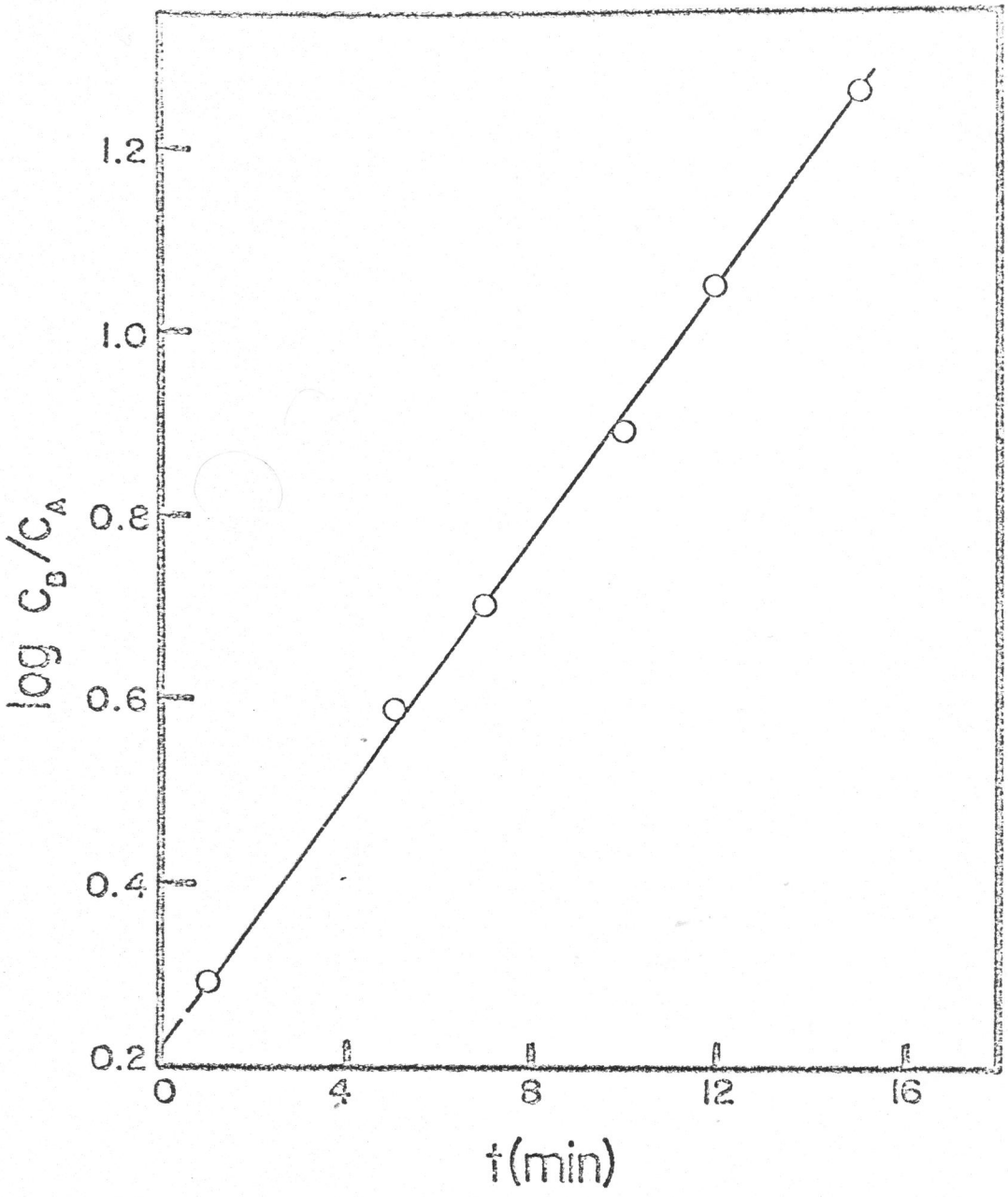


Figure 10. Second-order plot for the DMAP-catalyzed acetylation of isopropanol in the absence of pyridine. C^0_{DMAP} = 0.036 M. Data from Table IX.

For the catalytic action of DMAP in the presence of pyridine, the rate will be given by Equations 20-21.

$$V = \{k_{DMAP}[DMAP] + k_{PYR}[PYR]\}[ROH][Ac_2O] \quad (20)$$

$$V = \{k'_{DMAP} + k'_{PYR}\}[ROH][Ac_2O] \quad (21)$$

$$V = k_{obs}[ROH][Ac_2O] \quad (22)$$

Figure 11 shows the second-order plot for the data in Table IX (11). From the graph, k_{obs} was determined to be 0.016 M^{-1} sec^{-1}. Since k_{PYR} is known, k_{DMAP} could be calculated, and was found to be 0.39 M^{-2} sec^{-1}. The average of the two values for k_{DMAP} (in the absence and presence of pyridine) is 0.36 M^{-2} sec^{-1}.

The rate constant for NMIM catalysis, k_{NMIM}, is 7.6 x 10^{-3} M^{-2} sec^{-1}. Therefore, DMAP is about 47 times more effective than NMIM as a catalyst for this reaction. This is consistent with the observation that the concentration of catalyst required to complete the reaction in about 5 minutes is 0.1 M for DMAP and 4.7 M for NMIM.

6. Inhibition of NMIM Catalysis by Imidazole

On the basis of arguments presented in the introduction, imidazole was predicted to inhibit catalysis by NMIM. Table X shows the data for the time course of the

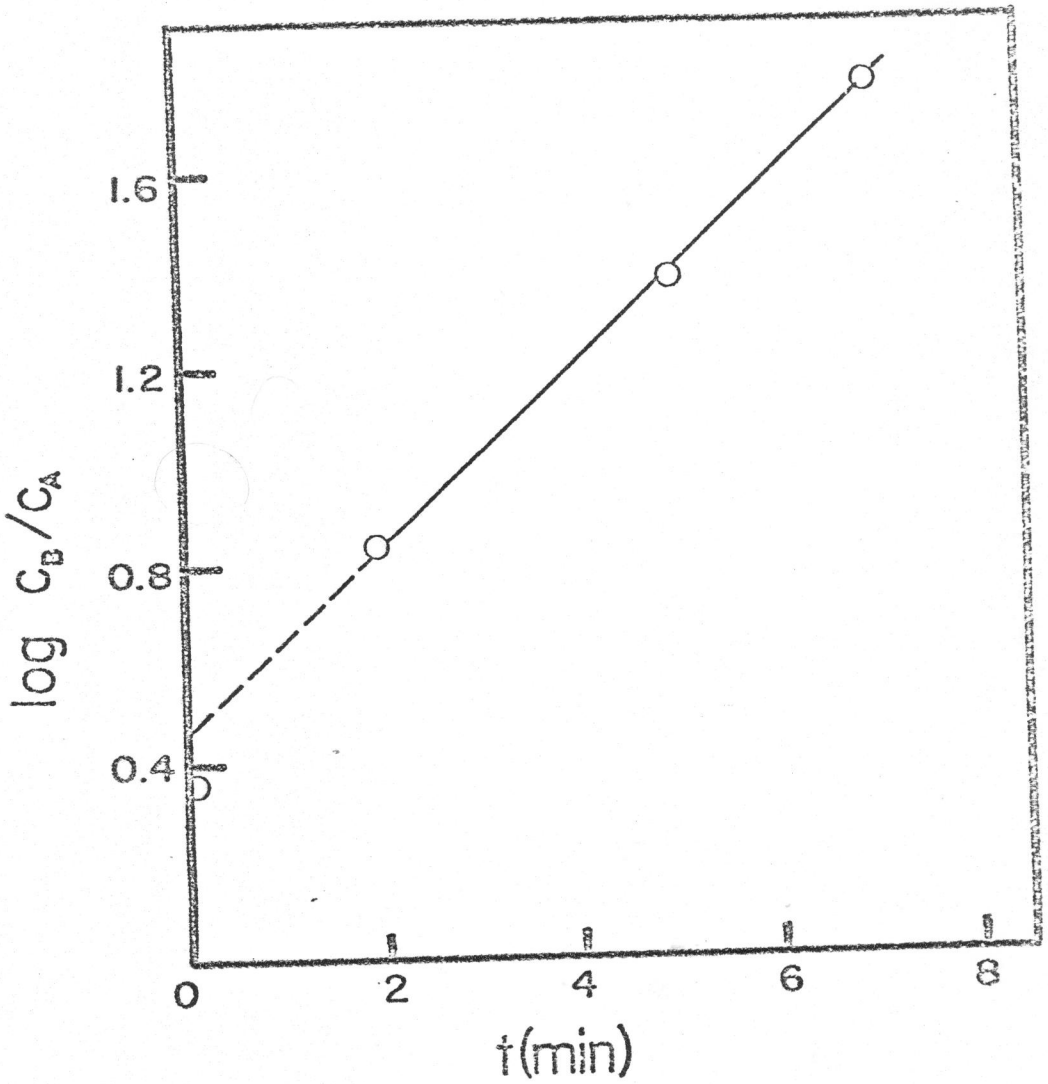


Figure 11. Second-order plot for DMAP-catalyzed acetylation of isopropanol in the presence of pyridine. C^0_{DMAP} = 0.04 M, C^0_{PYR} = 4.4 M. Data from Table IX.

Table X. NMIM-Catalyzed Acetylation of Isopropanol in the Presence of Imidazole[a]

t (min)	% Reacted
1.0	35.0
3.0	68.5
5.0	85.5
7.0	90.5
8.5	93.5
10.0	95.5
12.0	97.0
15.0	99.5

[a] $C^0_{NMIM} = 2.5$ M
$C^0_{imidazole} = 0.15$ M
$C^0_{Ac_2O} = 0.8$ M

NMIM-catalyzed reaction in the presence of imidazole. Figure 12 shows a plot of the data from Tables X and II. Imidazole is seen to inhibit the reaction.

7. Analytical Results

Based on the kinetic data, the analytical procedure described in the Experimental section was developed. Table XI lists analytical results for the NMIM-catalyzed acetylation of various hydroxy compounds. The accuracy and precision of the method are comparable with those of other acylation procedures (6, 35).

A yellow color, which progressively darkened with time, was observed in the blank, and limited the accuracy of the visual end-point detection. However, no significant alteration in the consumption of sodium hydroxide by the blank due to discoloration was observed. Hence, to improve end-point detection, it is recommended that the blank be maintained at 45° for three instead of seven minutes, as mentioned in the Experimental section for the analytical procedure. Very little or no discoloration was observed in the sample solution.

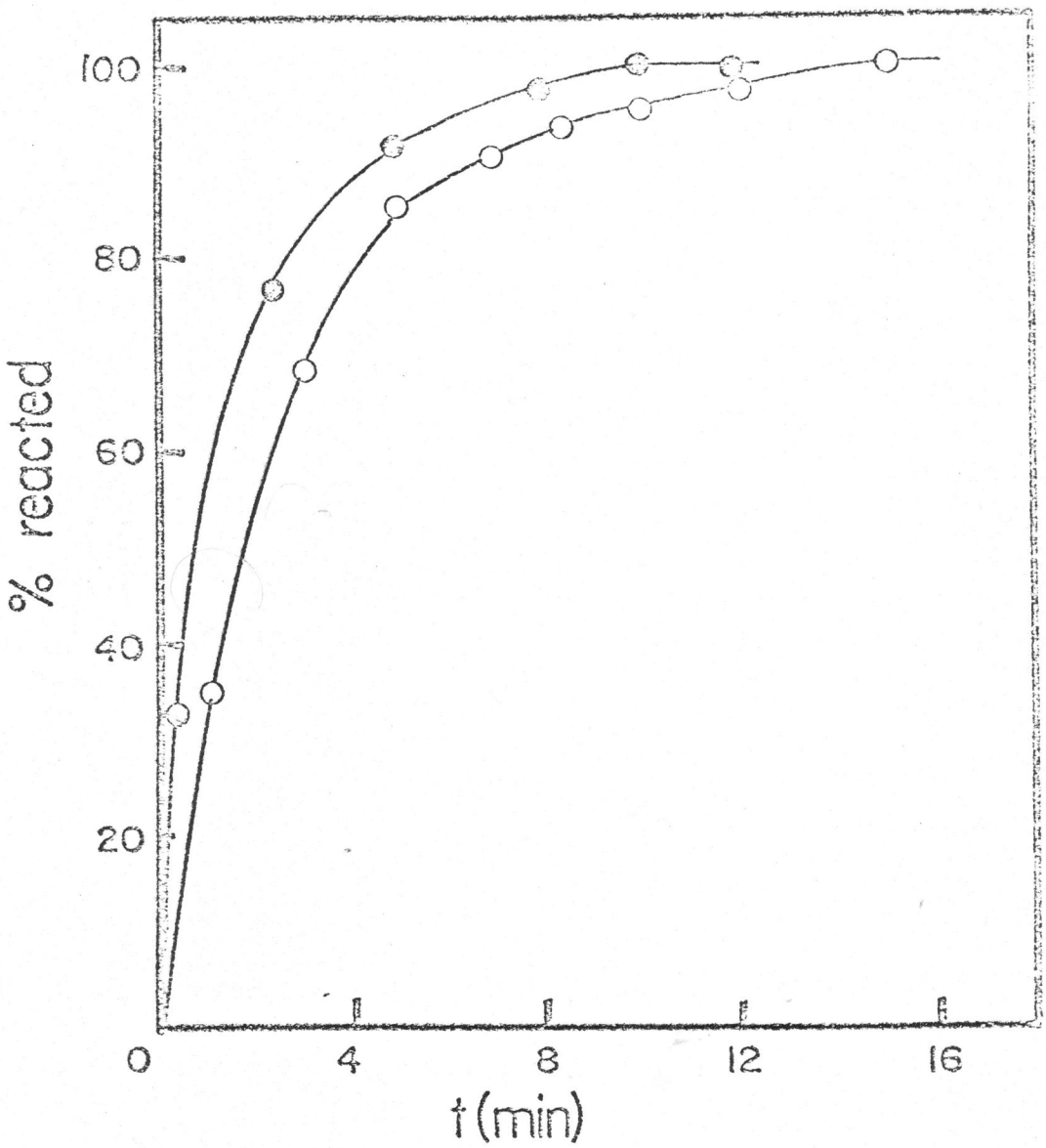


Figure 12. Time course for the NMIM-catalyzed acetylation of isopropanol at 45° in the presence and absence of imidazole. Key: ● , 2.5 M NMIM; and ○ , 2.5 M NMIM, 0.15 M imidazole.

Table XI. Analytical Results of NMIM-Catalyzed Acetylation of Some Hydroxy Compounds

Sample Compound	Mean Recovery (%)[a]	Standard Deviation, s (%)
Phenol	99.4	0.36
n-Propanol	99.9	0.26
n-Butanol	99.6	0.06
iso-Butanol	99.6	0.40
n-Amyl Alcohol	99.5	0.45
Isopropanol	99.6	0.40
sec-Butanol	99.8	0.32
1,2-Propanediol	99.2[b]	0.17
Ethylene Glycol	100.0[b]	0.10

[a]Mean of three determinations.

[b]Both hydroxy groups acetylated.

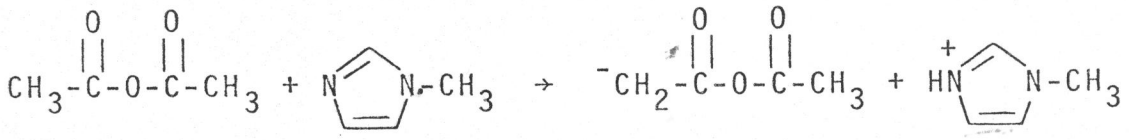
IV. DISCUSSION

The prediction that NMIM would catalyze acylations by Ac_2O and would be superior to pyridine as a catalyst in this reaction has been confirmed. The NMIM-catalyzed acetylation appears to be one of the most effective of available anhydride methods involving nucleophilic catalysis. Reaction times are short, precision and accuracy are good, and pyridine has been removed from the system.

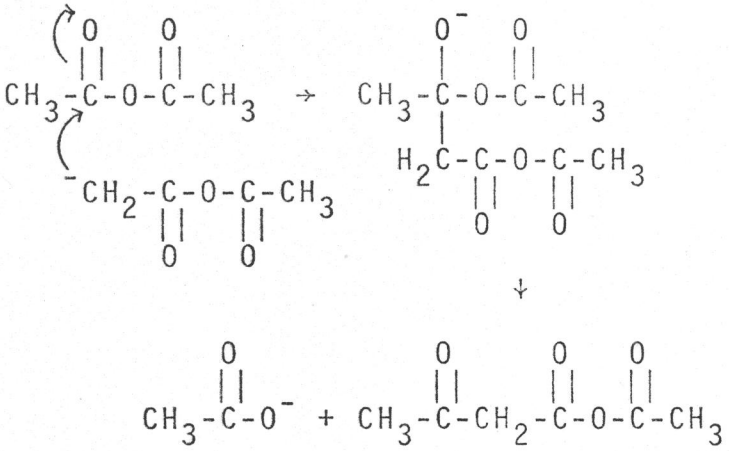
Some of the other results obtained and observations made are further discussed here.

1. Discoloration of Blank Solution

One limiting factor in the system is the discoloration observed in the blank solution. The progressively darkening yellow color may be a consequence of the possibility of C-acylation of Ac_2O by the catalyst in a Perkin-type condensation.



(23)



(24)

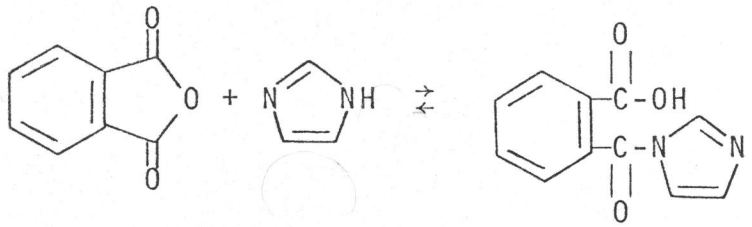
The condensation product contains an activated methylene group, and condensation may continue to finally yield a mixture of side products. Although the discoloration is a potential disadvantage, it has been minimized in the present system by modifying the analytical procedure as previously described.

2. Inhibition of Catalysis by Imidazole - Explanation

Imidazole was shown to inhibit the rate of acetylation of isopropanol by Ac_2O, as predicted in the introduction. However, Kingston, Garey and Hellwig (12) reported that the acylation of alcohols by pyromellitic dianhydride (PMDA) is catalyzed by imidazole. Although this is an apparent contradiction, the two phenomena, namely the inhibition of Ac_2O and catalysis of PMDA, are mechanistically consistent. Imidazole is anticipated to catalyze acylations by cyclic anhydrides and inhibit acylations by aliphatic anhydrides. For purposes of discussion, phthalic anhydride will be used

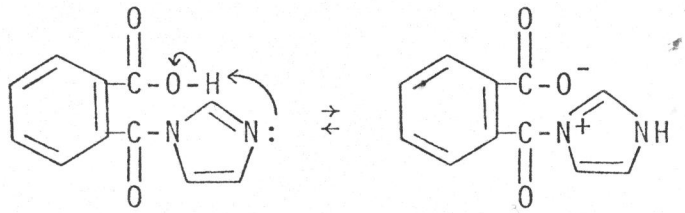
to represent the cyclic anhydrides.

The nucleophilic attack of imidazole on the cyclic anhydride will yield an acylimidazole having a 1,2 relationship with a carboxylic acid group, as shown in Equation 25.



(25)

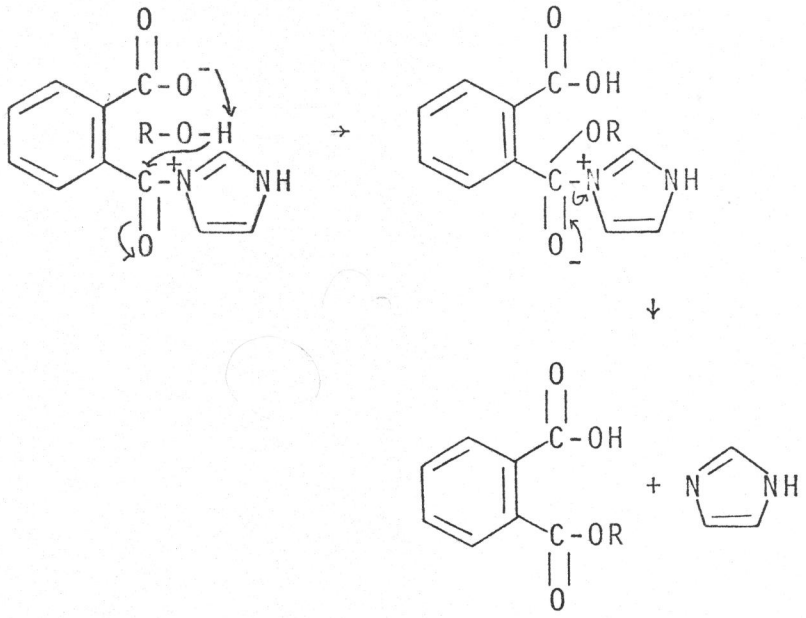
The product is fairly reactive due to this 1,2 relationship and the reverse reaction is apt to be favored. However, this also makes the product susceptible to nucleophilic attack through intramolecular participation. This is analogous to the hydrolysis of phthalamic acid (26), which is closely related in structure to the acylimidazole. One possible mechanism is the intramolecular transfer of a proton from the carboxylic acid function to the imidazole ring, converting it to the protonated acylimidazolium ion.



(26)

The product of this reaction is very reactive since it has a good leaving group, the neutral imidazole molecule.

Attack by a nucleophile such as an alcohol might be further facilitated by the general base carboxylate.



(27)

These equations indicate the possibilities, but the extent to which these processes are concerted or stepwise cannot be specified.

3. DMAP-Catalyzed Acetylation

Previous studies using DMAP as a catalyst have retained pyridine as a solvent and proton scavenger, as mentioned in the Introduction. This fact, and the discoloration produced at high DMAP concentrations, are the main drawbacks of the system. However, it was shown in the Results that DMAP catalyzes the acetylation of isopropanol equally efficiently in the absence and in the presence of pyridine.

The discoloration produced in the blank was not significant enough to cause problems in end-point detection. Therefore, DMAP can be used in the absence of pyridine to catalyze analytical acylations.

Connors and Albert (15) calculated third-order rate constants for the acetylation of isopropanol with Ac_2O using an Ac_2O/DMAP/pyridine system. The values they reported were $k_{DMAP} = 6.32 \times 10^{-2}\ M^{-2}\ sec^{-1}$ and $k_{PYR} = 3.53 \times 10^{-6}\ M^{-2}\ sec^{-1}$. These values are in error due to a miscalculation. The corrected values (re-calculated from their data) are $k_{DMAP} = 0.45\ M^{-2}\ sec^{-1}$ and $k_{PYR} = 2.5 \times 10^{-5}\ M^{-2}\ sec^{-1}$. These are in close agreement with the rate constants obtained in this study: $k_{DMAP} = 0.36\ M^{-2}\ sec^{-1}$ and $k_{PYR} = 2.1 \times 10^{-5}\ M^{-2}\ sec^{-1}$.

V. FURTHER STUDIES

1. NMIM Catalysis of Other Acylations

NMIM has been demonstrated to be superior to pyridine as a catalyst for the acetylation of hydroxy compounds. This finding can be extended to other substrates and acylating agents.

Lapshin et al. (30) have studied the kinetics of acetyl halide reactions with aromatic amines in the presence of NMIM, and reported that the nature of the counterion had major kinetic effects upon the rates of reaction of the $AcNMIM^+$ with the amines. Takaku et al. (31) reported that the phosphorylation of alcohols using NMIM and mercuric chloride as catalysts proceeds through the formation of an intermediate, the N-phosphoryl-N'-methylimidazolium salt. This in turn reacts with the alcohols to give the dihydrogen phosphates. The authors subsequently used this method to synthesize nucleotides (32).

Table XII (27) lists the acylating agents presently in use that incorporate pyridine as the catalyst, and the substrates for which they are used. An extension of the present work could study the effectiveness of NMIM in these systems.

Table XII. Acylating Agents Used in Analytical Chemistry with Pyridine as Catalyst

Reagent	Substrate	Finish	Reference
Acetic anhydride	Alcohols	Titration of unreacted anhydride after hydrolysis	4
Phthalic anhydride	Alcohols Amines	Titration of unreacted anhydride after hydrolysis	5
Pyromellitic dianhydride	Alcohols Amines	Titration of unreacted anhydride after hydrolysis	37
3,5-Dinitrobenzoyl chloride	Alcohols	Spectrophotometric measurement of ester in base	38, 39
p-Nitrobenzoyl chloride	Alcohols	Spectrophotometric measurement of ester	40
Succinic anhydride	Alcohols Amines	Titration of unreacted anhydride after hydrolysis	41

2. Analytical Finish

Another area offering room for improvement is the analytical finish of many acylation methods. A titrimetric end point measures the unreacted reagent and not the product. Since a direct measure of the product is often desirable, the spectrophotometric and fluorimetric determination of the reaction products might give greater selectivity and sensitivity. In this laboratory, the NMIM-catalyzed cinnamoylation of aromatic amines is presently being investigated using UV spectroscope (33). Acetylation of hydroxy groups is a common derivatization procedure prior to gas chromatographic separation. NMIM can be used as a catalyst and solvent for such acylations. Studies carried out in this laboratory indicate that NMIM is an effective catalyst for this purpose, and the method is useful in analyzing mixtures of hydroxy compounds (34).

3. DMAP as an Acylation Catalyst

DMAP warrants further investigation as an acylation catalyst since it is more powerful than NMIM. In addition, this study demonstrated that DMAP catalysis can be carried out in the absence of pyridine - this eliminates the major drawback of the DMAP system presently in use.

4. Study of Side Reactions

Many of the acylations catalyzed by nucleophilic compounds such as pyridine, DMAP, NMIM, and 2-pyridylacetic acid produce colored side products that interfere in the analysis. These side reactions deserve further study. Such a study would be fruitful both from the mechanistic and analytical points of view. It has been reported that the Ac_2O-pyridine reagent should contain 0.3-0.5% water to prevent a polymerization reaction (3), but literature records disagreement.

5. Intramolecular Catalysis

The concept of intramolecular catalysis in analytical acylations deserves further investigation, since mechanistic studies of intramolecularly catalyzed acyl transfers has shown that these reactions are extremely rapid compared to their intermolecular analogs (18-20).

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