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Quantitative acid-catalyzed acetylation

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QUANTITATIVE ACID-CATALYZED ACETYLATION

by

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INTRODUCTION

The simplest, most convenient method for the determination of the organic hydroxyl group is probably acetylation. In addition, it is a general method for the determination of amino groups and mercapto groups although in the majority of cases, phenols, amines, and mercaptans are more conveniently titrated in nonaqueous media.

The hydroxyl containing sample is usually heated with an excess of acetic anhydride, water is then commonly added to quench the reaction, and the resulting acetic acid is titrated with standard alcoholic sodium hydroxide:

$$(CH_3CO)_2O + ROH \longrightarrow CH_3COOR + CH_3COOH \qquad (1)$$

$$(CH_3CO)_2O + H_2O \longrightarrow 2\ CH_3COOH \qquad (2)$$

A blank containing exactly the same amount of acetic anhydride but no hydroxyl sample is treated similarly, and the difference between the titrations is equivalent to the amount of hydroxyl group present.

THE LITERATURE

Analytical Acetylations of Alcohols

The development of the acetylation method has centered around the use of acetic anhydride and has been reviewed by Mehlenbacher (23). Benedict and Ulzer (3) first acetylated samples of hydroxyl containing fatty acids by heating with acetic anhydride alone. André (1) modified the analysis by saponifying the sample before and after acetylation to determine the amount of acetate ester formed.

Verley and Bolsing (36) were the first to use pyridine as a solvent with a 12% solution of acetic anhydride. They also hydrolyzed the acetic anhydride to acetic acid and titrated it with sodium hydroxide. Later investigators retained the pyridine-acetic anhydride reagent and introduced modications such as use of n-butanol as homogenizer by West, Hoaglund, and Curtis (37). Ogg, Porter, and Willits (27) used a reagent concentration of 3 parts pyridine to 1 part of acetic anhydride in combination with n-butanol as homogenizer. These 30 to 60 minute macro and semimicro procedures are used by both Fritz and Hammond (12) and Siggia (30).

In fact, the use of pyridine has been so widely accepted that Guenther, Kulka, and Rogers (18) in a review objected to its omission in the acetylation method of Kepner and Webb (20).

In view of the above established procedures, it is not

difficult to understand that acetylation with acetyl chloride and acid-catalyzed acetylation, both more rapid methods, have been neglected. For instance, Smith and Bryant (32) analyzed more than 30 alcohols and phenols by heating with acetyl chloride in pyridine and toluene at 60° for only 20 minutes.

Analytical Acetylations of Phenols and Amines

In addition to the foregoing method for phenols, Siggia (30) has applied the Ogg, Porter, and Willits (27) method to the determination of phenols and monosubstituted phenols and has observed that 2,4,6-trisubstituted phenols react only very slightly with acetic anhydride in pyridine. Petersen, Hedberg, and Christensen (29) have determined resorcinol and nitrophenols on a micro scale at room temperature with 24 hour reaction periods. In any method for phenols, any unreacted, fairly acidic phenol is titrated as acetic acid by sodium hydroxide and hence causes a greater error in the determination.

The same acetylation procedures for alcohols and phenols are applicable to the determination of amines. However, the limitations are numerous. For instance Wild (38) has stated that dibutylamine, diarylamines, carbazole, pyrrole, and phenothiazine cannot be determined by acetylation. In addition, some amines or amides, such as 2,4,6-tribromoaniline

and p-nitroacetanilide, are very insoluble.

Siggia (30) has successfully applied the Ogg, Porter, and Willits (27) method to arylamines, monosubstituted arylamines, aliphatic amines, and aliphatic diamines. The Mitchell, Hawkins, and Smith (25) scheme of analyzing for water consumed in the hydrolysis of acetic anhydride by the Karl Fischer method is also applicable to the above amines.

The quantitative acetylation of deactivated anilines, such as the nitroanilines, has not been reported either. In particular, Hall (19) found o- and p-nitroanilines too weakly basic to titrate in nonaqueous solvents, and Fritz, Moye, and Richard (13) found them too weakly acidic to titrate in nonaqueous media. Although their quantitative acetylations are not in the literature, some kinetic rate data is available on the acylation of m- and p-nitroanilines. Litvinenko and Grekov (22) found the rate constants at 25° for the acetyl chloride acetylation of aniline and p-nitroaniline to be 1.16 and 0.00149, respectively; Kretov and Kulchitskaya (21) found the rate constants at 30° for maleic anhydride acylation of aniline and m-nitroaniline to be 2.9 and 0.023. The para isomer is about an order of magnitude less reactive than the meta isomer.

Acid-Catalyzed Acetylations

Acid-catalyzed acetylation on a preparative organic scale is not new. Fieser (9) gives directions for

acetylation of salicylic acid in pure acetic anhydride with 2 drops of sulfuric acid.

Conant and Bramann (6) studied the acid and base-catalyzed acetylation of b-naphthol in 0.88M acetic anhydride in glacial acetic acid and found that 0.2M perchloric acid catalyzed the reaction at an immeasurably fast rate. Using 3M pyridine as a standard, 0.2M sulfuric acid catalyzed the reaction 20 times as fast and 0.2 M p-toluenesulfonic acid 3 times as rapidly.

Acid-catalyzed acetylation has been employed by Toennies and Kolb (35). They used a 0.2 to 0.25 M solution of perchloric acid and of acetic anhydride in glacial acetic acid to acetylate hydroxyl groups in amino acids. The reaction required 2 hours at room temperature. A 3 hour reaction of anthranilic acid was needed to determine the excess anhydride.

Pesez (28) used a 0.17M solution of p-toluenesulfonic acid and 1.3M proprionic anhydride in glacial acetic acid for acid-catalyzed acylations for 2 hours at room temperature or 30 minutes at 100°. In an investigation of the proper concentration and ratio of acid to anhydride, Erdős and Bogati (8) found that a mole ratio of .001 to .01 chlorosulfonic acid to acetic anhydride was the optimum, and that 3 moles of acetic anhydride to 1 mole of alcohol was the proper ratio for rapid reaction. However, even at reflux, n-butanol required 6 hours for complete reaction.

Very recently, Mesnard and Bertucat (24) utilized

phosphoric acid-catalyzed acetylation at room temperature with a reagent consisting of 15 drops of 80% phosphoric acid, 10 ml. of acetic anhydride, and 20 ml. of dioxane. However, the acetylations were slow, methanol requiring 3 hours for quantitative reaction and ethanol 6 hours. Tertiary alcohols could be quantitatively acetylated in 24 hours. Phenols apparently could not be quantitatively acetylated at room temperature.

Physical organic studies have established that perchloric as well as sulfuric acid forms a very reactive acetylium ion, which is then capable of acetylating any hydroxyl group very rapidly. Gillespie (15) has demonstrated the presence of the acetylium ion by cryoscopic measurements of acetic anhydride in excess sulfuric acid. Burton and Praill (4) have established that perchloric acid is more effective than sulfuric in the formation of the acetylium ion. They have postulated the formation of an oxonium salt between aryl ethers and acetylium ions, and have carried out room temperature acetylations of anisole, using perchloric acid and acetic anhydride in glacial acetic acid (5).

The Burton-Praill (4) mechanism involves the formation of a reactive acetylium ion intermediate in equilibrium with acetic anhydride:

$$Ac_2O + H^+ \rightleftharpoons Ac_2OH^+ \rightleftharpoons Ac^+ + HOAc \qquad (3)$$

$$Ac^+ + ROH \longrightarrow ROAc + H^+ \qquad (4)$$

The equilibrium is shifted to the right by the reaction of any electrophile such as an alcohol with the acetylium ion. A proton is regenerated in reaction 4 and can rapidly re-establish the equilibrium. As long as the solvent is not basic and is dry, the acetylation proceeds at a rapid rate.

Barltrop and Morgan (2) have utilized this same perchloric acid catalysis in titrating water or primary alcohols in 0.06 to 0.1N perchloric acid with acetic anhydride in acetic acid as titrant, using an external ferric hydroxamate indicator. The titrimetric reaction was slow when water concentrations were above 20%, when ethers were used instead of acetic acid, or when the acid concentration fell to 0.04N. Chloroform and ethylene chloride inhibited the indicator color. Water could also be estimated in aniline, apparently because it formed the anilinium ion and acetylation was thus retarded.

Base-Catalyzed Acetylations

Gold and Jefferson (17) have proposed a mechanism for pyridine-catalyzed hydrolysis of acetic anhydride:

$$C_5H_5N + Ac_2O \rightleftharpoons C_5H_5NAc^+, OAc^- \qquad (5)$$

$$C_5H_5NAc^+ + H_2O \longrightarrow C_5H_5NH^+ + HOAc \qquad (6)$$

Reaction 5 was rate determining with the hydrolysis of the pyridine-acetylium ion being rapid in reaction 6. Pyridine,

3-methylpyridine, and 4-methylpyridine all catalyzed the hydrolysis rapidly and followed the Bronsted catalysis law. Steric hindrance with 2-methylpyridine or 2,6-dimethylpyridine inhibit the catalytic effect, and the Bronsted catalysis law is not obeyed.

EXPERIMENTAL

Development of the Method

Preliminary observations

Qualitative observations demonstrated that a rapid acetylation was taking place by mixing perchloric acid with pyridine, acetic anhydride and an alcohol.

This observation was tested by varying the concentration of perchloric acid in an acetic anhydride-pyridine reagent and holding all other conditions constant. The results are shown in Table 1 in the succeeding section. They definitely show that the acetylation is quantitative at room temperature and that heat was not needed to push the reaction to completion. This data prompted a wide investigation of the most favorable conditions for this acid catalysis.

Concentration of the anhydride

The limits for the concentration of anhydride are fixed by keeping the 0.55N NaOH titration of the hydrolyzed blank within 50 ml. and by using a low enough concentration of anhydride to permit use of a 5 ml. pipet. This is the concentration described by Fritz and Hammond (12); that is, 3 parts ethyl acetate or pyridine solvent to 1 part acetic anhydride, or about 2M acetic anhydride.

Concentration of perchloric acid

Table 1 contains data on the effect of increasing the

Table 1. Effect of molarity of $HClO_4$ on 10" acetylations of 2-ethylhexanol in 25:25 pyridine:acetic anhydride

M $HClO_4$	% Reaction
0	81
0.025	84
0.05	88.4
0.10	98.5
0.15	99.8

concentration of perchloric acid in 1:1 pyridine-acetic anhydride on 10 minute acetylations of 2-ethylhexanol.

In 3:1 ethyl acetate:acetic anhydride, the concentration of 0.15M perchloric acid is retained. If this concentration is doubled to 0.30M, erratic results of from 96.5 to 98.7% are obtained for 2-ethylhexanol. Calculations based on 5 ml. of this 0.30M reagent indicate that the water added with the perchloric acid reduces the amount of acetic anhydride available to react with 4 mmoles of alcohol from 12.5 to 9.5 mmoles. Even though 0.30M is an unsatisfactory concentration, the ratio of acid to anhydride in the 0.15M perchloric acid reagent is twice the ratio in the 1:1 reagent mentioned in Table 1. This ratio determines the concentration of the reactive acetylium ion in reactions 3 and 4.

Choice of solvent

Ethyl acetate is the solvent of choice because of the stability of acetic anhydride in it, its availability in pure

form, and the minimum color of the reagent. The titration of acetic acid after hydrolysis gives essentially constant values over a period of 2 weeks, and the anhydride content decreases only about 5%. Trialkyl phosphate reagents are equally stable.

The yellow color of the reagent darkens into orange sometime after 2 weeks, and this modifies the violet color of the end point to an undesirable green. When the reagent transmits less than 10% at 425 mu or 20% at 450 mu on a Beckman Model B spectrophotometer, it has undesirable color.

The reagent develops the minimum color as long as an equimolar amount of anhydride is first added to react quickly with all the water in the perchloric acid and any alcohol in the ethyl acetate, at room temperature. Then the remaining anhydride is added cold to the cooled reagent. If all the anhydride and ethyl acetate-perchloric acid are mixed while cold, the destruction of water seems to accelerate condensation of impurities in the presence of excess acetic anhydride.

The rate of acetylation in dimethoxyethane, chloroform, or trialkyl phosphates is similar to that in ethyl acetate. However, the glycol ether contains peroxides which apparently cause a dark brown color in the reagent unless the glycol ether is freshly distilled. The color of a chloroform or trialkyl phosphate reagent is much lighter yellow than the ethyl acetate reagent, but chloroform is more volatile than ethyl acetate. Ethyl benzoate, diethyl malonate, and

acetonitrile reagents develop unsatisfactory colors. Dimethyl sulfoxide is too basic to be mixed safely with 72% perchloric acid.

Morgan (26) mentions the use of ethyl acetate as a solvent for acetic anhydride although perchloric acid is added only at the time of reaction.

Where ethyl acetate is used as a solvent for the alcohol sample, the same amount is added to the reagent blank since ethyl acetate apparently contains a small amount of alcohol.

Comparison of pyridine and ethyl acetate

Table 2 demonstrates that an ethyl acetate reagent is far more reactive than a pyridine reagent and that perchloric acid definitely catalyzes acetylation in pyridine as well as in ethyl acetate at room temperature. Acetylation in ethyl acetate is quantitative in 5 minutes even for the sterically hindered 2-t-butylcyclohexanol, which reacts very slowly in the pyridine reagent.

Table 2 also demonstrates that pyridine without acid catalyzes room temperature acetylation of the unhindered primary and secondary alcohols tested. In general the primary alcohols react rather rapidly with the acid-catalyzed pyridine reagent and are quantitatively acetylated in 5 minutes. Secondary alcohols vary in reactivity depending on steric hindrance to acetylation and react quantitatively in from 10 to 30 minutes or longer.

Table 2. 5 minute acetylations of 4 mmoles alcohol with 1:1 solvent:acetic anhydride

Alcohol	No acid-% reaction		0.15M $HClO_4$ % reaction	
	EtOAc	Pyridine	Pyridine	EtOAc
Methyl	66	87	100	100
Ethyl	25	45	100	100
Neopentyl	17	38	95	100
Isopropyl	5	10	80	100
Diisobutyl carbinol	2	7	64	100
Cyclohexanol	0	0	75	100
2-Methylcyclohexanol	0	0	60	100
2-t-Butylcyclohexanol	0	0	7	100
t-Butyl	0	0	0	70 (Limit)

Comparison of monoprotic acid catalysts

Table 3 contains a comparison of the catalysis of various monoprotic acids with that of perchloric acid. Perchloric is the most effective acid catalyst although p-toluenesulfonic is almost as effective and has utility in an ethyl acetate reagent since it does not give high results with tetrahydrofurfuryl alcohol, as does perchloric, as shown in Table 8.

Reaction time

The effect of varying reaction times on the percentage recovery for amyl and neopentyl alcohols in ethyl acetate is

Table 3. Monoprotic 0.15M acid catalysis in five minute acetylation of 4 mmoles cyclohexanol with 3:1 solvent:acetic anhydride

Acid	EtOAc - % reaction	Pyr. - % reaction
$HClO_4$	100	75
HCl	100	30
p-$MePhSO_3H$	65	60
Cl_3CCOOH	5	13
HNO_3	4	55
None	1	ca.5

Table 4. Varying reaction time for 4 mmole 1^o alcohol with 0.15M $HClO_4$ in 3:1 ethyl acetate:acetic anhydride

n-Amyl (ca. 98%)		Neopentyl (ca. 99%)	
time-min.	% reaction	time-min.	% reaction
5	97.4	10	99.0
4	97.3	5	100.3
2	95.2	4	97.2
1	95.2	2	89.5
1/2	92.0		

shown in Table 4. The reaction is extremely rapid and appears to be almost instantaneous because the times include pipeting time. Probably the rate of mixing and/or dissolving controls the speed of the reaction. In pyridine, primary

Table 5. Reagent hydrolysis time: 5 ml. of 3:1 ethyl acetate:acetic anhydride

Time (min.)	Temp.	Ml. pyr. ml. H_2O	Ml. 0.55N NaOH
17	r.t.	5/3	61.43
10	r.t.	5/3	61.40
10	r.t.	0/3	54.55
5	50°	5/3	61.47
4	r.t.	9/3	61.47

alcohols react in 5 minutes, and secondary alcohols react in from 10 to 30 minutes.

Hydrolysis of acetic anhydride

Conventional methods consist in heating in pyridine to catalyze the hydrolysis of acetic anhydride:

$$(CH_3CO)_2O + H_2O \xrightarrow[\triangle]{C_5H_5N} 2\ CH_3COOH \qquad (7)$$

However, as long as the pyridine to water volume ratio is about 3:1, the anhydride hydrolyzes satisfactorily in 5 minutes at room temperature, as is shown in Table 5.

Reagents

2M ethyl acetate reagent

For instant use, add 0.8 gm. (0.47 ml.) of 72% perchloric acid to 30 ml. of ACS grade anhydrous ethyl acetate

in a 50 or 60 ml. flask. The flask may be cooled in cold water and stirred magnetically as 10 ml. of ACS grade acetic anhydride is pipeted into it. (Caution: never add perchloric acid to acetic anhydride as the acid catalyzes a sometimes violent surface reaction of its water of hydration with the anhydride.)

For permanent quantity use, add 4 gm. (2.35 ml.) of 72% perchloric acid to 150 ml. of ACS grade anhydrous ethyl acetate in a clean, acetone-free 250 ml. glass stoppered flask. Then pipet in 8 ml. ACS grade acetic anhydride, which is sufficient to react with all the water in the 72% perchloric acid, and allow to stand at room temperature for at least 30 minutes. Cool both the flask and a bottle of acetic anhydride to 5°, add 42 ml. more of the 5° acetic anhydride, keep the flask at 5° for an hour, and allow the reagent to come to room temperature before use. It will develop a yellow color owing to impurities in the acetic anhydride, but the color and the stability of the anhydride are satisfactory for about 2 weeks. Over that period, a typical 5 ml. aliquot of reagent may vary from 26.86 to 26.78 meq. acetic acid after hydrolysis, and from 11.3 to 10.85 meq. acetic anhydride by the usual aniline methods.

Pyridine, ethyl benzoate, and freshly distilled dimethoxyethane are suitable solvents for instant use although acetylation in pyridine is slower. Chloroform and trialkyl phosphates are suitable for both instant and permanent use,

and both reagents are much lighter in color than an ethyl acetate reagent.

2M pyridine reagent

Follow directions for 2M acetylating reagent based on 30 ml. ethyl acetate, but use 30 ml. of reagent grade pyridine instead of ethyl acetate. Cautiously add the 72% perchloric acid dropwise to the pyridine. This reagent should be prepared fresh daily as it discolors after about 6 hours and the acetic acid blank decreases about 3% after 24 hours. The reagent can be stored at 5° and kept overnight with the formation of a light violet color and only a 0.5% decrease in the acid blank.

For 3M pyridine reagent, follow the above directions, but use 20 ml. of pyridine, 10 ml. acetic anhydride, and 0.47 ml. 72% perchloric acid.

Reagents for sodium hydroxide titration

Sodium Hydroxide, 0.55N: To 185 ml. of saturated aqueous sodium hydroxide, add 430 ml. of water and 5400 ml. of methyl cellosolve (Union Carbide Chemicals Co.) or 5400 ml. absolute methanol. The reagent blank requires about 49 ml. of 0.55N sodium hydroxide titrant. The only satisfactory procedure for using methyl cellosolve is to use only unopened cans since leaving the solvent stand after the can has been opened and closed allows enough aldehydes to form to cause a yellow color in the sodium hydroxide titrant. Methyl

cellosolve tends to leak less from a buret and to evaporate more slowly than methanol.

Mixed indicator: Mix 1 part of 0.1% neutralized aqueous cresol red with 3 parts of neutralized thymol blue. For 50 ml. of 0.1% indicator, weigh out 12 mg. of cresol red, 37 mg. of thymol blue, dissolve in 50 ml. of water, and neutralize with any solution of dilute base to a violet color.

Potassium Acid Phthalate: Primary standard grade.

Procedure

Normal, non-acidic compounds

Weigh a sample containing from 3 to not more than 4 mmoles of hydroxyl into a 125 ml. glass stoppered flask and pipet exactly 5 ml. of 2M acetylating reagent (10 mmoles of acetic anhydride) into the flask. Insoluble solids or immiscible liquids (such as glycerol) should be stirred until dissolution occurs. Allow to react at room temperature at least 5 minutes. Weakly basic amines require longer. Add about 1 to 2 ml. water from a squeeze bottle, shake, add 10 ml. of 3:1 pyridine:water, and allow to stand 5 minutes. Titrate with 0.55N alcoholic sodium hydroxide using mixed indicator, from a yellow to a violet end point. Dark colored samples can be titrated to an apparent pH of 9.8 using glass-calomel electrodes and a pH meter.

Run a reagent blank by adding exactly 5 ml. of

acetylating reagent to a 125 ml. flask containing 1 to 2 ml. water. Add 10 ml. of 3:1 pyridine:water, allow to stand 5 minutes, and titrate as above.

Caution: in order to be doubly careful regarding possible perchloric acid explosion, do not heat any acetylating solution containing perchloric acid, and dispose of solutions promptly when determinations are finished. Heating samples with perchloric acid is not recommended. Dilute perchloric acid in acetic acid and even in acetic anhydride as solvent has been safely used for years in the field of non-aqueous titrations.

Standarize the 0.55N sodium hydroxide against potassium acid phthalate to the same end point.

Use the difference between the blank, V_b, and the sample titration, V_s, to calculate the percentage of hydroxyl compound in the sample.

$$\% \text{ OH compound} = \frac{(V_b - V_s)\ (N_{NaOH})\ (\text{MEQ. wt.})}{\text{Sample wt., mg.}} \qquad (8)$$

Procedure for ethylsulfonylethanol

Since ethylsulfonylethyl acetate possesses a slightly acidic hydrogen which blurs the end point in the sodium hydroxide titration and causes low results, a different procedure is used in place of the final sodium hydroxide titration. After the 5 minute acetylation period, add 10 ml. of

a 1.5M distilled N-methylaniline solution in chlorobenzene to the flask instead of water and the water-pyridine solution. After 15 minutes, titrate the excess N-methylaniline potentiometrically with 0.3N perchloric acid in glacial acetic acid, using lithium chloride in glacial acetic acid in a sleeve calomel electrode.

React exactly 5 ml. of the acetylating reagent similarly with 10 ml. of the N-methylaniline solution and titrate potentiometrically as above. Fit the difference between the volume required for the reagent blank and for the sample into the above equation with the normality of the perchloric acid to find the percentage of the hydroxyl compound.

The above method is only applicable to water-free samples since it measures the amount of unreacted acetic anhydride.

Acetylation Samples

Purification of samples

Many of the compounds were samples from chemical companies. Some were Eastman white label chemicals. Most liquid alcohols were fractionally distilled through a 24 inch Podbielniak partial reflux fractional distillation column, using vacuum distillation if necessary. Many of the solids were vacuum sublimed. The methods of purification and any analyses carried out on the compounds are listed in

Tables 6 and 7. The amines and phenols were treated in the same manner.

Analysis of 2-t-butylcyclohexanol

While it was assumed that all the 2-substituted cyclohexanols were mixtures of cis and trans isomers, the mixture of cis and trans-2-t-butylcyclohexanols was analyzed by infrared analysis to demonstrate the content of this mixture. The compound was first vacuum sublimed twice; the first fraction showed a carbonyl impurity, but the second fraction was pure although it contained less of the cis isomer as is shown in Figure 1.

The infrared analysis of this second fraction was carried out using the 10.34 micron band mentioned by Goering, Reeves, and Espy (16). The trans isomer had a band at 9.47 microns but is transparent at 10.34. The pure cis isomer was furnished by Prof. Goering; 26.3 and 30.5 mg. per 10 ml. samples were analyzed and % transmittances found to be 45 and 39. A 37.6 mg. per 10 ml. solution of the second fraction was analyzed and the % transmittance found to be 44. All readings were subtracted from 100 and 15 units were subtracted from these numbers to correct for a 100% transmittance line, giving 40, 46, and 41 units, respectively. Linear interpolation between 46 and 40 gave 27 mg. or 72% cis isomer in the mixture.

Table 6. Purification methods and physical properties of alcohols

Alcohol	Purification, purity (lit.)	Mp. or bp. (lit.)°C	$n_D^{25°}$ (lit.)
Isoamyl	Fr. dst.	130	1.4052
Benzoin	99.2% (14)	-	-
Benzoin oxime	Cryst.	-	-
cis-2-Buten-1,4-diol	Fr. dst.	89 (1 mm.)	1.4752
t-Butyl	Fr. dst.	81	1.3854 (1.3878)
2-t-Butylcyclohexanol	Vac. sbl.	44-5 (cis 54-5)	-
t-Butyl hydroperoxide	88.9% (12)	-	-
Cinnamyl	Dst., Vac. sbl.	110 (3 mm.)	-
Cyclohexanol	Fr. dst.	95 (20 mm.)	1.4635 (1.4626)
2-Cyclohexylcyclohexanol	Fr. dst.	98 (1 mm.)	1.4990
Diisobutyl carbinol	Fr. dst.	76 (5 mm.)	1.4210 (1.4242)
Dimethylbenzyl	Fr. dst.	66 (4 mm.)	1.5204
2,5-Dimethyl-2,5-dihydroperoxyhexane	94.8% (12)	-	-
Diphenylcarbinol	Cryst., Et_2O	67.8 (68-9)	-
Ethyl	None	-	-
2-Ethylhexanol	Fr. dst.	99 (5 mm.)	1.4298
Ethylsulfonylethanol	Cryst., $CHCl_3$, CCl_4	41.5-3 (40-2.5)	-
Furfuryl	Fr. dst.	167	1.4838 (1.4868)
Glycerol	96.5% (33)	-	-
Methyl	None	-	-
2-Methylcyclohexanol	Fr. dst.	50 (1 mm.)	1.4623 (cis 1.4633)
Neopentyl	Fr. dst.	54-5.5 (55-6)	- trans 1.4597)
2-Phenylcyclohexanol	Fr. dst.	98 (1 mm.)	1.5339
Propargyl	None	-	1.4305
Isopropyl	Dst. fr. $NaBH_4$	-	-

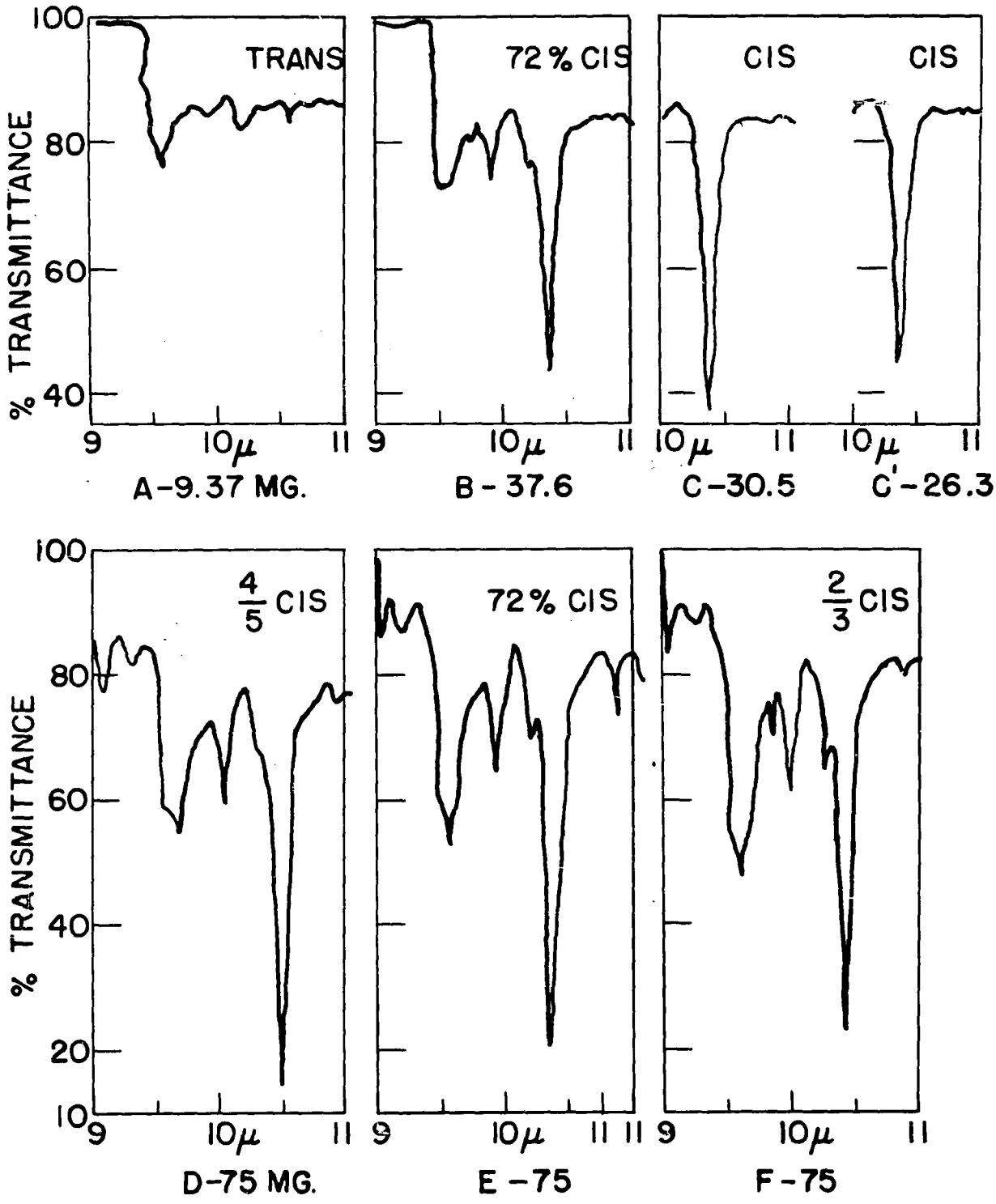
Table 6. (Continued)

Alcohol	Purification, purity (lit.)	Mp. or bp. (lit.)°C	$n_D^{25°}$ (lit.)
Tetrahydrofurfuryl	Fr. dst.	175	1.4499 (1.4499)
2,2,2-Trifluoroethanol	Fr. dst.	73.5	- (1.2895)
Triphenylcarbinol	98.0% (11)	161-2 (162.5)	-
2,2,4-Trimethyl-pentan-1,3-diol	Vac. sbl.	49-50 (49-51)	-

Table 7. Purification and properties of phenols, amines, etc.

Compound	Purification, purity	Mp. or bp. (lit.)°C, $n_D^{25°}$
Aniline	Dst.	45 (2 mm.), 1.5823
Diphenylamine	Cryst., Pet.	53-4 (53)
N-Methylaniline	Dst.	60 (2 mm.), 1.5679
o-Nitroaniline	Vac. sbl.	70-1 (71.5)
m-Nitroaniline	Cryst., Bz.	114-5 (114)
p-Nitroaniline	Vac. sbl.	148-9 (147.5)
o-t-Butylphenol	Fr. dst.	74 (1 mm.), 1.5209
2,6-Di-t-butyl-p-cresol	Cryst., MeOH	69-70 (62-8)
p-Methyoxyphenol	Eastman W. L.	53-4 (53)
2,3-Naphthalenediol	Cryst., NaOH	162-3
Resorcinol	Cryst., Et_2O, Bz.	109-10 (110)
t-Butyl mercaptan	98% min.	-
Cyclohexanone oxime	Eastman W. L.	-
Lactose	U.S.P.	-

Figure 1. Perkin Elmer Infracord infrared curves of 2-t-butylcyclohexanol isomers in 10 ml. of CS_2. A shows trans band at 9.47; C and C' show 10.34 cis band used in analyzing B. D, E (and B), and F are the first sublimate, second sublimate, and bottoms of a Dow Chemical sample; D showed a carbonyl impurity at 6.0 microns.


100
80
60
40
% TRANSMITTANCE
TRANS
72% CIS
CIS
CIS
9
10μ
11
A-9.37 MG.
B-37.6
C-30.5
C'-26.3
20
4/5 CIS
72% CIS
2/3 CIS
D-75 MG.
E-75
F-75

RESULTS

Alcohols and Glycols

Table 8 presents analytical data for the quantitative acetylation of various alcohols and glycols in ethyl acetate

Table 8. Analysis of 1° and 2° alcohols and glycols in EtOAc in 5"

Alcohol	Average	Remarks
Isoamyl	98.1 ± 0.2	
Cinnamyl	98.5 ± 0.4	Pyr., EtOAc - 94%
Ethyl	99.1 ± 0.5	
2-Ethylhexanol	99.4 ± 0.2	
Ethylsulfonylethanol	98.9 ± 0.2	
Furfuryl	99.2 ± 0.2	Pyr., EtOAc - Polym.
Methyl	99.9 ± 0.3	
Neopentyl	98.0 ± 0.3	
Propargyl	100.1 ± 0.3	Pyr. or EtOAc
Tetrahydrofurfuryl	97.5 ± 0.5	Pyr., EtOAc - 112%
Trifluoroethyl	98.9 ± 0.6	
2-t-Butylcyclohexanol	99.5 ± 0.6	
Benzoin	99.3 ± 0.3	
Benzoin oxime	99.7 ± 0.1	3M pyr., 15"
Cyclohexanol	100.1 ± 0.3	
2-Cyclohexylcyclohexanol	98.6 ± 0.3	
Di-isobutylcarbinol	100.5 ± 0.1	
Diphenylcarbinol	100.3 ± 0.3	
2-Methylcyclohexanol	102.9 ± 0.3	
2-Phenylcyclohexanol	102.2 ± 0.4	
Isopropyl	100.3 ± 0.3	
cis-2-Buten-1,4-diol	98.8 ± 0.4	Pyr.
Glycerol	97.1 ± 0.5	
2,2,4-Trimethylpentan-1,3-diol	100.5 ± 0.1	
Tris (hydroxymethyl) amino-methane	98.5 ± 0.1	3M pyr.

Table 9. Analysis of phenols, amines, hydroperoxides, etc.

Compound	Average		Remarks
o-t-Butylphenol	101.9	0.2	5-20", No nucl. acetylation
2,6-Di-t-butyl-p-cresol	100.4	0.5	5-20", " " "
p-Methoxyphenol	102.2	0.1	5-20", " " "
2,3-Naphthalenediol	102.7	0.7	
Resorcinol	100.5	0.8	
Diphenylamine	101.8	0.9	45", Nuclear acetylation
o-Nitroaniline	101.3	0.2	30"
m-Nitroaniline	100.2	0.3	20"
p-Nitroaniline	99.3	0.4	60"
t-Butyl hydroperoxide	88.7	0.3	Pyr., 10"
2,5-Dimethyl-2,5-dihydroperoxy-hexane	94.9	0.4	Pyr., 10"
t-Butyl mercaptan	100.4	0.3	10", 0°, Aliquot in EtOAc
Cyclohexanone oxime	99.5	0.1	3M pyr., 15"
Lactose	101.3	0.5	

in 5 minute reaction times. Where pyridine reagent is used, this is noted. Regardless of steric hindrance or electronic properties, all alcohols were immediately acetylated. In the case of benzoin oxime, both the alcoholic hydroxyl group and the oxime hydroxyl group were acetylated.

Phenols, Amines, and Miscellaneous

Phenols were acetylated in 5 minutes as shown in Table 9 regardless of steric hindrance; high results were not observed with such compounds as p-methoxyphenol even though longer reactions times were deliberately used. Such nuclear acetylation was observed with diphenylamine where the per cent acetylation increased slowly with time. The nitroanilines required from 20 to 60 minutes reaction time, no great improvement over standard acetylation in pyridine. The end point in the sodium hydroxide titrimetric finish for resorcinol was vague and broad, and the precision was thus poor.

Mixtures

Tertiary alcohols such as t-butyl alcohol and α,α-dimethylbenzyl alcohol do not react at room temperature in the pyridine reagent. A number of primary and secondary alcohols were determined in the presence of these alcohols as is shown in Table 10, using times of 10 minutes for primary alcohols and 20 to 60 minutes for secondary alcohols. Slightly longer

Table 10. Analysis for 1° or 2° alcohols in 3° alcohols in pyridine

1° or 2° alcohol-time"		3° alcohol-meq.		% recovery % purity
Methyl	7	t-Butyl	-4	99.1
"		"	8	99.3
2-Ethylhexanol	10	"	4	100.5
"		"	8	100.7
Cyclohexanol	18	"	4	99.9
"		"	8	100.3
Isopropyl	20	"	4	99.0
"		"	8	99.7
Neopentyl	10	Dimethylbenzyl	-4	100.0
"		"	8	100.1
2-Methylcyclo-hexanol	60	"	4	99.9
"		"	8	100.7
Cyclohexanol	20	2-t-Butylcyclohexanol	-10 mol%	100.7
"		"	20 mol%	101.6
"		"	30 mol%	106.5

reaction times were required for the mixtures than for pure compounds because 2 ml. of pyridine was added to each mixture. More hindered secondary alcohols such as 2-cyclohexylcyclohexanol would probably require longer reaction times than 2-methylcyclohexanol in the pyridine reagent. Table 10 also contains data on the determination of cyclohexanol in 72% cis-2-t-butylcyclohexanol using the pyridine reagent. As the

Table 11. Analysis for resorcinol in hindered phenols in pyridine-20"

Hindered phenol-meq.		% recovery resorcinol four meq.
o-t-Butylphenol	-4	109
"	2	98.5
"	1	99.8
2,6-Di-t-butyl-p-cresol	-4	98.0
"	2	99.6
"	1	98.0

concentration of the latter is increased, more of the trans isomer is present to react with the pyridine reagent and the determination becomes merely an estimation.

Table 11 contains data on the determination of resorcinol and presumably other phenols in the presence of hindered phenols in the pyridine reagent. Apparently when the concentration of o-t-butylphenol becomes appreciable, it reacts slightly during the 20 minute reaction period and causes high results. Both phenols are too weak to interfere with the base titration.

Interferences

Water

In ethanol-water mixtures, perchloric acid catalyzes the acetylation of ethanol even though more water is present

Table 12. Effect of H_2O on acetylation of EtOH (11 mmole Ac_2O)

mmoles EtOH	mmoles H_2O	wt. % EtOH	% Reaction
4.0	6.6	63	100.6
3.8	7.0	58	99.6
3.4	10.0	47	93.7
3.5	12.0	43	80.3

than the amount of anhydride added in a 5 ml. aliquot of ethyl acetate reagent. Burton and Praill (4) report a similar catalytic effect. However, for quantitative recovery of the ethanol, it is necessary to have a definite excess of anhydride over water, as is shown in Table 12.

By increasing the concentration of acetic anhydride to a 1:1 solvent:anhydride ratio (4M), it should be possible to determine as low as 25 wt.% solutions of ethanol in water.

Functional groups

Because acetylation in ethyl acetate probably proceeds through a reactive positive species and because the reagent contains perchloric acid, a number of functional groups, such as the carbonyl group, interfere to varying degrees.

The interference of simple ketones, such as acetone, is eliminated by chilling sample and reagent to 0° or by using the pyridine reagent. Cyclic ketones which are somewhat

enolic, such as cyclohexanone, interfere even at 0°, but do not interfere with acetylation in pyridine. Aldehydes interfere seriously in both ethyl acetate and pyridine; Fritz and Hammond (12) report that aldehydes also interfere with the standard method of acetylation in hot pyridine. The carbonyl group in benzoin, however, does not interfere with acetylation of the alpha-hydroxyl group.

Table 13 summarizes the other important interferences such as double bonds and the tetrahydrofuran ring. The triple bond of propargyl alcohol does not appear to interfere with acetylation in either solvent as the results in Table 8 demonstrate. Only benzene rings activated by a hetero atom, such as oxygen in 1,3-dimethoxyethane, constitute an interference in ethyl acetate.

Since tertiary alcohols react about 70% in the ethyl acetate reagent, tertiary hydroperoxides are better analyzed with the pyridine reagent in case appreciable amounts of tertiary alcohols are present.

Ethylsulfonylethanol acetylates quantitatively, but the acetate possesses an acidic hydrogen which is partially titrated by NaOH. Hence, N-methylaniline in chlorobenzene is added to react with the excess anhydride, and the excess N-methylaniline is then titrated with perchloric acid in glacial acetic acid.

Tris(hydroxmethyl)aminomethane is insoluble in the ethyl acetate reagent, but all 3 hydroxyl groups and the amino

Table 13. Interferences tested with alcohols or alone

Interference - mmoles		% Reaction of alcohol EtOAc	Pyr.
Benzaldehyde	4	270 - 0°	93
Formaldehyde	12	-	129
Formic acid	8	-	147
Acetone	2	99.5	-
"	20	100.0 - 0°	99
Diethyl ketone	12	114,101.0 - 0°	98.8
Cyclohexanone	4	155 - 0°	98.0
Cyclopentanone	4	109 - 0°	99.0
Acetophenone	12	100.0	-
Benzene	16	99.5	-
Toluene	16	100.0	-
Durene	16	100.5	-
m-Dimethoxybenzene	4	146	99.5
Compounds tested alone			
Acetylacetone[a]		56(30"),106 (70")[b]	-
Dibenzoylmethane[a]		61(15"),104 (80")[b]	-
Diethyl malonate		6(60")[b]	-
Ethyl cyanoacetate		6(60")[b]	-
Cinnamyl alcohol		94	98.1
1,3-Dimethoxybenzene		56	NR
Ethylsulfonylethanol[a]		60-92	-
Furfuryl alcohol		Polymer	99.2
Indene		94 (45")	NR
Isobutyraldoxime		150	75
Maleic hydrazide		78 (30")	-
Nitromethane[a]		NR[b]	-
Phthalimide		32 (60")	-
Tetrahydrofurfuryl alc.		118	97.5
Thiourea		3	-
Triphenylmethane		NR	-
Urea		NR	-

[a]Fugitive end point in sodium hydroxide titration.

[b]Determined with N-methylaniline and perchloric acid.

group acetylate rapidly in a 2:1 pyridine:anhydride (3M) reagent. Oximes appear to interfere non-stoichiometrically in ethyl acetate, but at least ketoximes are acetylated quantitatively in pyridine.

RESULTS AND DISCUSSION SUPPORTING PUBLISHED MECHANISMS

A number of experiments were carried out that support, but do not in themselves establish exclusively mechanisms in the literature. These results are grouped together to clarify, establish, and extend the scope of the method and interferences.

Nitrogen Bases

The mechanistic hydrolysis of the pyridine-acetylium ion proposed by Gold and Jefferson (17) can be modified for a reaction with alcohols, preceded by acid catalysis to form an equilibrium amount of the pyridine-acetylium ion:

$$Ac_2O + C_5H_5NH^+ \rightleftharpoons C_5H_5NAc^+ + HOAc \qquad (9)$$

$$C_5H_5NAc^+ + ROH \longrightarrow C_5H_5NH^+ + ROAc \qquad (10)$$

Support for the pyridine-acetylium ion is in the next section.

The pyridinium ion may dissociate into a proton and pyridine, and catalyze the formation of the pyridine-acetylium ion in reaction 9 via the following steps:

$$C_5H_5NH^+ \rightleftharpoons C_5H_5N + H^+ + Ac_2O \rightleftharpoons Ac_2OH^+ \qquad (11)$$

$$Ac_2OH^+ + C_5H_5N \rightleftharpoons C_5H_5NAc^+ + HOAc \qquad (12)$$

The acetic anhydrium ion probably does not dissociate into

the free acetylium ion but reacts reversibly with the pyridine.

Reaction 10 is sensitive to steric hindrance as are all displacement reactions. In pyridine primary alcohols acetylate in 5 minutes, secondary alcohols in 10 to 60 minutes, and tertiary alcohols not at all. Apparently tertiary alcohols are too bulky to displace the pyridine molecule from the pyridine-acetylium ion. Reaction 10 seems to be rate determining for secondary and tertiary alcohols, but the equilibrium represented in reaction 9 may be the slow step in acetylation of the primary alcohols. Hence primary and secondary alcohols can be determined in the presence of tertiary alcohols. In fact, as is shown in Table 10, cyclohexanol and other more reactive alcohols can be estimated in the presence of small amounts of the slow reacting, bulky 2-tert-butylcyclohexanol, a secondary alcohol.

Comparison of Basic Solvents

Table 14 illustrates the effect of steric hindrance around the basic nitrogen for perchloric acid-catalyzed acetylation in basic solvents. Acetylation proceeds at similar rates in 3- and 4-methylpyridines and in pyridine, but it is considerably slower in 2-methylpyridine, 2,6-dimethylpyridine, and dimethylaniline. The nitrogen atom is, hence, definitely involved in the rate-determining step.

Table 14. 5 Minute acetylations of 4 mmoles alcohol with 3:1 basic solvent:acetic anhydride, 0.15M perchloric acid

Solvent	EtOH-% reaction	Cyclohexanol-% reaction
Pyridine	100	86
2-Methyl-pyridine	39 (35°)[a]	5 (35°)[a]
3-Methyl-pyridine	93	85
4-Methyl-pyridine	100	92
2,6-Dimethyl-pyridine	30 (45°)[a]	-
Dimethylaniline	26	7
Dimethylacetamide	10	1

[a]The pyridinium perchlorates of these samples were insoluble at room temperature and the reagents and samples had to be heated to the specified temperatures to retain homogeneity.

In fact, acetylation of ethanol in pyridine with no perchloric acid present is actually faster than in the latter 3 solvents. Acid-catalyzed acetylation of ethanol in dimethylacetamide is slower than uncatalyzed acetylation of ethanol in ethyl acetate with no acid present, suggesting that amides inhibit acid-catalyzed acetylation.

Aprotic or Neutral Solvents

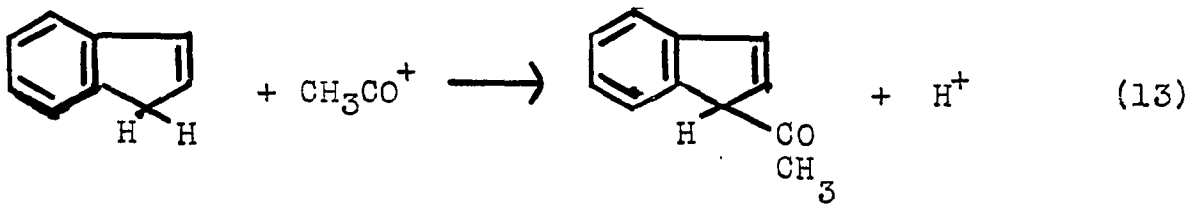
The Burton-Praill (4) mechanism involves the formation of a reactive intermediate, the acetylium ion, which should react rapidly and irreversibly with an electrophile. Hence

as long as the medium is not basic and is dry, an unhydrated proton ought to catalyze acetylation of an alcohol or phenol at roughly the same rate, irrespective of solvent. The presence of acetic anhydride insures the absence of any water which would hydrate a proton.

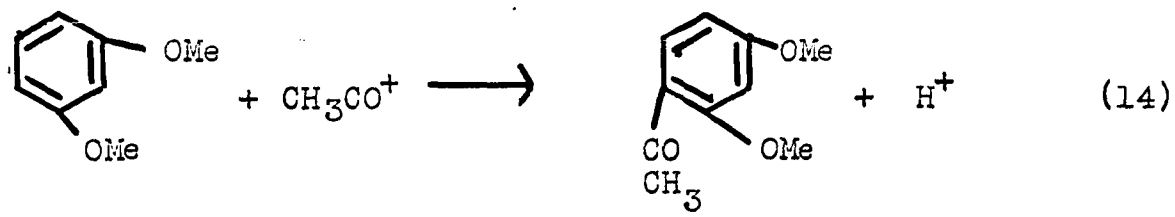
The fact that the acetylation of all alcohols and most of the phenols is quantitative in 5 minutes indicates that a reactive species is an intermediate. This is especially true considering the steric hindrance in cis-2-t-butylcyclohexanol and 2,6-di-t-butyl-p-cresol. Table 4 shows that acetylation of simple alcohols is so rapid that it is almost instantaneous. By the nature of its size, the acetylium-pyridine ion acetylates the former compounds only slowly.

Acetylation of 2-t-butylcyclohexanol in five minutes was used as a test of the speed of acetylation in various solvents. Acetylation in chloroform, triethyl phosphate, ethyl acetate, and dimethoxyethane was virtually complete, indicating that the reaction path was virtually independent of the neutral solvent used.

Burton and Praill (4) found evidence for the existence of the acetylium ion by isolating considerable amounts of p-methoxyacetophenone from mixtures of the acetylating reagent and anisole. Table 13 indicates that both indene and m-dimethoxybenzene are 94 and 56% acetylated, respectively, probably undergoing the following reactions:



(13)



(14)

The fact that acetylation at reflux temperatures in pyridine or acid-catalyzed acetylation in pyridine at room temperature do not proceed through the intermediate acetylium ion is indicated by the fact that neither indene nor m-dimethoxybenzene are acetylated under either condition. The pyridine-acetylium ion is apparently not capable of nuclear acetylation.

Adding an aliquot of acetylating reagent containing 11 meq. of anhydride to a mixture of 12 meq. of water and 3.5 meq. of alcohol should hydrolyze most of the anhydride and preclude appreciable acetylation, if the anhydride molecule were the acetylating species. However, as Table 12 shows, 80% of the alcohol is acetylated. This result is consistent with the random instantaneous reaction of the acetylium ion on colliding with either water or alcohol. Apparently the reagent must remain dry and acid catalysis must remain effective until all the anhydride is destroyed.

Transesterification

Acetylation in esters such as ethyl acetate might involve a transesterification or ester interchange:

$$Me\text{-}C_6H_{10}OH + EtOAc \xrightarrow{H^+} EtOH + Me\text{-}C_6H_{10}OAc \qquad (15)$$

If this is the case, the speed of acid-catalyzed acetylation would be due to the rapid acetylation of a simple primary alcohol, ethanol, instead of a hindered alcohol such as 2-methylcyclohexanol.

This possibility was tested by preparing a 0.15M solution of dry perchloric acid in ethyl acetate with enough acetic anhydride being added to destroy all the water present in the acid and all the alcohol present in the ethyl acetate. This reagent was added to separate samples of 2-methylcyclohexanol and t-butyl alcohol, and the mixtures were allowed to stand for an hour. A 2M solution of acetic anhydride in pyridine was added for a 5 minute reaction period.

The 2-methylcyclohexanol was 47% acetylated, compared to a 60% acetylation when acid-catalyzed acetylation in pyridine was employed. The t-butyl alcohol failed to react as it did under similar conditions in pyridine. If appreciable transesterification had taken place, a greater degree of acetylation would have been found. Of course, the fact that acid-catalyzed acetylation takes place as rapidly in solvents which are not esters also mitigates against a

transesterification mechanism being the sole mechanism.

Triphenylcarbinol and Diphenylcarbinol

Diphenylcarbinol and presumably other alcohols can be estimated in the presence of triphenylcarbinol with the ethyl acetate reagent, provided there is an excess of perchloric acid catalyst over the amount of triphenylcarbinol present. The triphenylcarbinol or triphenylmethyl acetate consumes an equimole amount of perchloric acid in ionizing quantitatively to the stable colored triphenylcarbonium ion, and the water released is then removed by reaction with acetic anhydride:

$$Ph_3COH + H^+ \longrightarrow Ph_3C^+ + H_2O \xrightarrow{Ac_2O} 2HOAc \qquad (16)$$

Fritz and Fulda (11) have utilized the same reaction in titrating triphenylcarbinol in acetic anhydride with perchloric acid.

Experiments with less perchloric acid present than triphenylcarbinol consistently gave incomplete acetylations of diphenylcarbinol as shown in Table 15. Triphenylcarbinol does undergo some acetylation before it dehydrates, and the determination of any alcohol in its presence is, hence, an estimation unless the triphenylmethyl acetate is hydrolyzed in acid. Triphenylsilanol probably does react with the acetic anhydride, but the silyl acetate hydrolyzes rapidly in water, releasing acetic acid rather than forming a triphenylsiliconium ion.

Table 15. Acetylation of Ph_2CHOH in Ph_3COH or Ph_3SiOH with 2M or 3M acetic anhydride in ethyl acetate (15")

Mmoles Ph_2CHOH	Mmoles PH_3COH	Mmoles $HClO_4$	% reaction
1	0.5	0.8	99.50[c]
2	1	1.6	102.5, 104
3.5[a]	1.5[a]	0.8	82, 92
3.5	1.5	0.8	88, 89
2.5	2.5[b]	0.8	99.9
0	0.8	0.8	12 (15, 30")
0	0.5	0.8	0[c]

[a]Solid mixture dissolved in EtOAc before reagent added.

[b]Triphenylsilanol.

[c]Water only added to hydrolyze the Ph_3COAc.

If there is no rapid equilibrium between perchloric acid and the acetylium ion in reaction 3, all the perchloric acid should be consumed in cases where triphenylcarbinol is in excess over the acid. However, at least 80% of diphenylcarbinol is acetylated before this occurs. This indicates that the reaction and establishment of the equilibrium are probably more rapid than the dehydration in reaction 16, and possibly that the equilibrium in reaction 3 lies to the right, since the acetylium ions must be generated over 3 times to acetylate at least 80% of the diphenylcarbinol.

It is interesting that triphenylcarbinol acetylates about 12% in ethyl acetate reagent regardless of the time of

Table 16. Acetylation of Ph_3COH and t-BuOH in various solvents containing 0.75 meq. $HClO_4$ (15")

Solvent	% reaction 0° 3 mmoles t-BuOH	% reaction 1 mmole Ph_3COH
EtOAc	70	16[a]
EtOBz	99.5	18[a]
$(EtOOC)_2CH_2$	-	10[a]
$(BuO)_3PO$	92	81
$(MeO)_2C_2H_4$	64	30[a]
CH_3CN	89	23
PhCl	-	31[a]
$CHCl_3$	99.5	14[a]

[a]An immediate yellow color occurred as the reagent was added, and a ppt. of the yellow salt followed. In the other solvents, color formation was slower.

reaction. This indicates that either the acetylium ion is present and acetylates the hydroxyl group, or more probably that the equilibrium is rapid enough to generate acetylium ions, before the protons are consumed in the slower dehydration which stops acetylation. The triphenylmethyl acetate is also ionized by acid.

This effect was studied in different solvents and only in tributyl phosphate was a nearly quantitative acetylation observed, as shown in Table 16. Adding dry perchloric acid in tributyl phosphate to triphenylcarbinol and then adding

a tributyl phosphate reagent gave only 12% acetylation, demonstrating that dehydration can take place in this solvent. Hence, in tributyl phosphate the equilibrium must be established extremely rapidly and may lie farther to the right than in the other solvents. Ionization of triphenylmethyl acetate may also be slow in this solvent.

Tertiary butyl alcohol was analyzed in various solvents by slowly pipeting a chilled solution of the alcohol into a rapidly stirred chilled reagent so as to minimize dehydration and allow time for regeneration of the acetylium ion. The results in Table 16 indicate ethyl benzoate and chloroform are suitable solvents for the estimation of alkyl tertiary alcohols.

DISCUSSION

Rate of Acetylation in Neutral and Basic Solvents

Acetylation in aprotic or neutral solvents is more rapid than in basic solvents. Assuming that the concentration of the hydrogen ion controls the rate of acetylation in either type of solvent, it is of interest to compare these concentrations. All of the perchloric acid in the neutral solvents is potentially available as hydrogen ions so that the concentration of hydrogen ions would be 0.15M. The perchloric acid in the pyridine-acetic anhydride solvent is present as the pyridinium ion; if water were present, the pyridinium ion could ionize in this way:

$$C_5H_5NH^+ + H_2O \rightleftharpoons C_5H_5N + H_3O^+ \qquad (17)$$

Since acetic anhydride and not water is present, reaction 11 can be assumed to represent the ionization of the pyridinium ion, forming the acetic anhydrium ion. The concentration of the acetic anhydrium ion can be calculated crudely by assuming that the K_a of 7×10^{-6} for the pyridinium ion in water is the same in the pyridine-acetic anhydride solvent, and assuming that the same ionization constant expression for water can be written for this solvent system:

$$Ac_2OH^+ = \frac{K_a\ (C_5H_5N)}{(C_5H_5NH^+)} = \frac{7 \times 10^{-6}(9)}{(0.15)} = 4 \times 10^{-7} \qquad (18)$$

If it is assumed that most of the acetic anhydrium ion is converted into the pyridine-acetylium ion as in reaction 12, then the minimum concentration of the acetylating species is of the order of 10^{-7}M. The concentration of the acetylium ion in neutral solvents cannot be readily found, but some indication has been given above at least for tributyl phosphate that most of the 0.15M acid is possibly converted to the acetylium ion; the maximum concentration of the acetylium ion in tributyl phosphate would be of the order of 10^{-1}M. If the rate constants for acetylation in both types of solvents are similar, then the rates ought to differ by a maximum of a factor of 10^{6}. This may vary with the steric properties of an alcohol because the rate determining step for the acetylation of a hindered alcohol in pyridine may not be the same as for a primary alcohol such as ethanol.

Acetylations in neutral solvents, then, are rapid compared to acetylations in basic solvents, but are limited by side reactions with other electrophiles. Acetylations in pyridine at room temperature are relatively slow but have the advantage of very few interferences in that a less reactive species is probably present in small concentration and is generated by a rapid enough equilibrium to be analytically useful.

Acetylation of Alcohols

Table 8 presents analytical data for the quantitative acetylation of various alcohols and glycols in ethyl acetate in 5 minute reaction times. Regardless of steric hindrance or electronic properties, all alcohols were immediately acetylated. The average precision of the method is 0.3%. The accuracies ranged from 98 to 100% in most cases. A number of compounds were checked for purity by other methods, and the difference was never greater than 0.5%.

Acetylation in ethyl acetate is very advantageous for sterically hindered alcohols such as the 2-substituted cyclohexanols. Both 2-phenylcyclohexanol and 2-cyclohexylcyclohexanol are quantitatively acetylated in 45 minutes by standard methods of heating in pyridine-acetic anhydride on an 80° steam bath. The 2-t-butylcyclohexanol used in this research is only 84% acetylated in 45 minutes and 99% acetylated in 60 minutes by standard methods.

While it is assumed that all the 2-substituted cyclohexanols used consisted of a mixture of cis and trans isomers, the 2-t-butylcyclohexanol used was analyzed by infrared methods and found to be about 72% of the cis isomer. Goering, Reeves, and Espy (16) noted qualitative acetylation at 0° at 2 hours for the trans isomer, but at 2 days for the cis isomer. The cis isomer, in which the steric interaction due to the bulk of the t-butyl group precludes the chair

conformation of an equatorial t-butyl group, possess the hydroxyl group in the hindered, less easily esterified axial position. Acid-catalyzed acetylation in pyridine for 1 hour of the mixed cis and trans isomers used gave 26% reaction, a fair estimate of the amount of trans isomer present and an indication of the unreactivity of the cis isomer; 2-methylcyclohexanol, for instance, is quantitatively acetylated in 1 hour.

Acetylation of Tertiary Hydroperoxides

Tertiary hydroperoxides can be safely and conveniently analyzed at room temperature with the acid-catalyzed pyridine reagent, whereas existing methods which require heating in pyridine would tend to decompose some of the hydroperoxide before it is completely acetylated. Since tertiary alcohols are a likely impurity, it is preferable to use the pyridine reagent rather than the ethyl acetate reagent which would react with the tertiary alcohol. Tertiary alcohols are not affected by the pyridine reagent. If it were not for the presence of tertiary alcohols, tertiary hydroperoxides could probably be analyzed in ethyl acetate since they would not be expected to dehydrate as easily:

$$H_2C{=}CMe_2 + H_2O_2 \underset{?}{\overset{H^+}{\longleftarrow}} {}^tBuOOH + Ac_2O \xrightarrow{H^+} {}^tBuOOAc \;\&\; HOAc \quad (19)$$

The dehydration would involve the extrusion of hydrogen

peroxide which would not appear to be as feasible as the extrusion of water in the case of tertiary alcohols.

Hydrogen peroxide and peroxy acids might also be acetylated if the acetyl peroxide and peroxides formed were stable to the basic titrant used.

Silbert and Swern (31) have acetylated hydroperoxides in pyridine and ether on a preparative scale.

Acetylation of Amines

Acetylation of amines in neutral solvents is retarded by buffering of the perchloric acid catalyst by the amine. In cases where the amine is too weakly basic to be an effective buffer, such as the case of diphenylamine, the acetylation is slow because diphenylamine possesses resonance structures in which the nitrogen's lone pair electrons are found in either benzene ring. For this same reason it is subject to nuclear acetylation.

2,2'-Dipyridylamine, the pyridine analog of diphenylamine, would not be expected to undergo nuclear acetylation as a side reaction. However, the tertiary pyridine nitrogens form the unreactive, insoluble pyridinium salts and no acetylation takes place in ethyl acetate. Even though tributyl phosphate dissolves the pyridinium salts, only 6% acetylation takes place in 30 minutes.

Aniline and N-methylaniline acetylate readily in neutral

solvents even though their anilinium ions are certainly formed, because only 20% as much perchloric acid as aniline is added, and the free base can then be acetylated. Initially some acetylium ions may be present and will react immediately with the free base. When 80% of the aniline is acetylated, the remaining 20% present as the anilinium ion must be supplied by equilibrium dissociation. Probably the mechanism is similar to reaction 11. After this point, the farther along the reaction proceeds, the more acid available to form acetylium ions and the faster the reaction should take place.

The nitroanilines acetylate as slowly in neutral solvents as in refluxing pyridine-acetic anhydride reagent. The o and p-nitroanilines both possess resonance structures in which the nitrogen's lone pair electrons are not available for reaction. p-Nitroaniline requires 45 minutes for acetylation by standard methods.

Acetylation of Phenols

Acetylation of phenols is not complicated by buffering effects as is acetylation of amines. However, any unreacted phenol is either titrated or renders the sodium hydroxide titration less sharp. In case the phenolic anion is colored, the indicator change is smeared.

Acid-catalyzed acetylation of 2,6-disubstituted phenols

is rapid and quantitative; however, this is not so for acetylation in refluxing pyridine. Some nuclear acetylation might be expected from such compounds as 2,6-di-t-butyl-p-cresol or p-methoxyphenol, but none was found even though reaction time was extended from 5 to 20 minutes. Nuclear acetylation of p-methoxyphenol might possibly have been expected because m-dimethoxybenzene was acetylated over 50% in that time.

Acetylation of resorcinol and 2,3-naphthalenediol are advantageous because nonaqueous titration generally only yields a single break for such phenols. The anion of 2,3-naphthalenediol is red, and any unreacted compound smears the sodium hydroxide titration end point so that the N-methylaniline-perchloric acid titrimetric finish must be used.

Oximes, Sugars, and Mercaptans

Acetylation of sugars in neutral solvents appears to be as rapid as acetylation of alcohols. Lactose is acetylated in 5 minutes although it gives slightly high results, which are probably due to opening of the glucopyranose ring.

Ketoximes such as benzoin oxime or cyclohexanone oxime are conveniently determined in pyridine at room temperature. Acetylation of cyclohexanone oxime and isobutyraldoxime in neutral solvents yields high results, presumably from addition across the oxime double bond. Snyder, Levin, and Wiley (34) report such additions to anils on a synthetic basis:

$$Ac_2O + PhN{=}{=}CR_2 \longrightarrow \underset{\underset{Ac}{|}}{PhN}\text{--}\underset{\underset{OAc}{|}}{CR_2} \qquad (20)$$

T-Butyl mercaptan is also acetylated in ethyl acetate quantitatively without elimination of H_2S. Apparently the fact that the sulfur atom in this compound is less basic, and therefore, less easily protonated prior to possible H_2S elimination, than the oxygen atom in t-butyl alcohol explains this phenomenon.

Mixtures

The pyridine reagent is a mild enough acetylating reagent at room temperature so that primary and some unhindered secondary alcohols can be acetylated in the presence of tertiary alcohols. Tertiary butyl alcohol and α,α-dimethylbenzyl alcohol do not react appreciably in mixtures of 50 and 66 mole % with primary and secondary alcohols, as shown in Table 10. Delahy and Sabetay (7) have also determined primary and secondary alcohols in the presence of tertiary alcohols. However, their results show 2% reaction in 2 cases and 10% reaction in another case.

As shown in the previous section, diphenylcarbinol and presumably other alcohols can be estimated in the presence of triphenylcarbinol or triphenylsilanol. The triphenylcarbinol is ionized to the stable triphenylcarbonium ion which cannot be acetylated.

Cyclohexanol and presumable other faster reacting alcohols can also be estimated in the presence of not more than 30 mole % of the 2-t-butylcyclohexanol used. Since the latter contains about 28% of the reactive trans isomer, this isomer presumably reacts enough to cause high results in pyridine. Presumably cyclohexanol could be accurately determined in the presence of pure cis-2-t-butylcyclohexanol.

Simple phenols such as resorcinol can be estimated in the presence of hindered 2 or 2,6-t-butylphenols, by using acid-catalyzed acetylation in pyridine. The end points are vague because of the presence of these weakly basic phenols and the precision is probably $\pm$ 1%.

SUMMARY

1. Acid-catalyzed acetylation was investigated and a perchloric acid-catalyzed method developed which is simpler and far more rapid than existing procedures.
2. Acetylation in neutral solvents such as ethyl acetate is quantitative in 5 minutes at room temperature for primary and secondary alcohols, phenols, and simple amines. Weakly basic amines require longer reaction times. Tertiary alcohols partially dehydrate.
3. Acetylation in basic solvents such as pyridine is quantitative in 5 minutes at room temperature for primary alcohols, 10 to 60 minutes for secondary alcohols, 10 minutes for hydroperoxides, 15 to 25 minutes for phenols, and 15 minutes for ketoximes.
4. Acetylation in pyridine can be used to assay primary or secondary alcohols in tertiary alcohols and simple phenols in o-t-butylphenol or 2,6-di-t-butyl-substituted phenols. Acetylation in ethyl acetate can be used to assay diphenylcarbinol in triphenylcarbinol.
5. Chief interferences in both solvents are aldehydes. Ketones interfere in ethyl acetate, but the interference of simple slightly enolic ketones can be eliminated at 0°. Aromatic compounds with activated rings also interfere in ethyl acetate.

6. Mechanisms are suggested for the reactions in both types of solvents, and support for these mechanisms is presented.
7. Acetylation in neutral solvents is rapid, has wide scope, but is a very drastic procedure where large amounts of interferences are present. Acetylation in basic solvents is slower but is a relatively mild procedure which permits differentiating determinations and avoids many interferences.

LITERATURE CITED

1. André, E. Compt. rend. 172, 984 (1921).

2. Barltrop, J. A. and Morgan, K. J. Anal. Chim. Acta 16, 520 (1957).

3. Benedict, S. R. and Ulzer, F. Monatsh. 8, 41 (1887).

4. Burton, H. and Praill, P. F. G. J. Chem. Soc. 1950, 1203.

5. _____ and _____ J. Chem. Soc. 1951, 522.

6. Conant, J. B. and Bramann, G. M. J. Am. Chem. Soc. 50, 2305 (1928).

7. Delahy, R. and Sabetay, S. Bull. soc. chim. France 1935, 1716.

8. Erdós, J. B. and Bogati, A. G. Rev. soc. quim. Mex. 1, 223 (1957). (Abstracted in Chem. Abstr. 52, 14523 (1958).)

9. Fieser, L. F. "Experiments in Organic Chemistry," D. C. Heath and Company, New York. (1941).

10. Fritz, J. S. "Acid-Base Titrations in Nonaqueous Solvents," G. F. Smith Chemical Co., Columbus, Ohio. (1952).

11. _____ and Fulda, M. O. Anal. Chem. 25, 1837 (1953).

12. _____ and Hammond, G. S. "Quantitative Organic Analysis," John Wiley and Sons, Inc., New York. (1957).

13. _____, Moye, A. J., and Richard, M. J. Anal. Chem. 29, 1685 (1957).

14. _____, Yamamura, S. S., and Bradford, E. C. Anal. Chem. 31, 260 (1959).

15. Gillespie, R. J. J. Chem. Soc. 1950, 2997.

16. Goering, H. L., Reeves, R. L., and Espy, H. H. J. Am. Chem. Soc. 78, 4926 (1957).

17. Gold, V. and Jefferson, E. C. J. Chem. Soc. 1953, 1409.

18. Guenther, E., Kulka, K., and Rogers, J. A. Anal. Chem. 29, 630 (1957).

19. Hall, H. K. J. Phys. Chem. 60, 63 (1956).

20. Kepner, R. E. and Webb, A. D. Anal. Chem. 26, 925 (1954).

21. Kretov, A. E. and Kulchitskaya, N. E. Zhur. Obshchei Khim. 25, 2474 (1955). (Abstracted in Chem. Abstr. 50, 9314 (1956).)

22. Litvinenko, L. M. and Grekov, A. P. Voprosy Khim. Kinetiki 1955, 860. (Original not available for examination; abstracted in Chem. Abstr. 50, 9348 (1956).)

23. Mehlenbacher, V. C. "Organic Analysis," Vol. 1, Interscience Publishers, Inc., New York. (1953).

24. Mesnard, P. and Bertucat, M. Bull. soc. chim. France 1959, 307.

25. Mitchell, J., Hawkins, W., and Smith, D. M. J. Am. Chem. Soc. 66, 782 (1944).

26. Morgan, K. J. Anal. Chim. Acta 19, 27 (1958).

27. Ogg, C. L., Porter, W. L., and Willits, C. O. Ind. Eng. Chem., Anal. Ed. 17, 394 (1945).

28. Pesez, M. Bull. soc. chim. France 1954, 1237.

29. Petersen, J. W., Hedberg, K. W., and Christensen, B. E. Ind. Eng. Chem., Anal. Ed. 15, 225 (1943).

30. Siggia, S. "Quantitative Organic Analysis via Functional Groups," John Wiley and Sons, Inc., New York. (1954).

31. Silbert, L. S. and Swern, D. Am. Chem. Soc. Abstracts of Papers 134, 3P (1958).

32. Smith, D. M. and Bryant, W. M. D. J. Am. Chem. Soc. 57, 61 (1935).

33. Smith, G. F. "Analytical Applications of Periodic Acid and Iodic Acid," G. F. Smith Chemical Co., Columbus, Ohio. (1950).

34. Snyder, H. R., Levin, R. H., and Wiley, P. F. J. Am. Chem. Soc. 60, 2025 (1938).

35. Toennies, G. and Kolb, J. J. J. Biol. Chem. 144, 219 (1942).

36. Verley, A. and Bolsing, F. Ber. 34, 3354 (1901).

37. West, E. S., Hoaglund, C. L., and Curtis, G. J. Biol. Chem. 104, 627 (1934).

38. Wild, F. "Estimation of Organic Compounds," Cambridge University Press, London. (1953).

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