ANALYSIS OF MIXTURES OF ALCOHOLS BY ACYLATION

By

William Dean Fellows
J. S. Fritz

November, 1961

Ames Laboratory
Iowa State University
Ames, Iowa

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F. H. Spedding, Director, Ames Laboratory

Work performed under Contract No. W-7405-Eng-82.

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ABSTRACT

Recently a general chemical method for the analysis of mixtures of alcohols appeared, using pyridine catalyzed acetylation and second order kinetics to determine the amount of the faster reacting component. The use of 0.25M isobutyric anhydride in pyridine containing 0.0025M perchloric acid as catalyst promotes the rate of the reaction and diminishes the time necessary to perform an analysis. A mathematical treatment of the data and kinetic plot reduces the number of kinetic points to only four or five. The mixtures are primarily composed of isomers.

A conventional plot of the second order reaction data is made. A plot of $\log \frac{(b - x)}{(a - x)}$ is made versus time, where b and a are the initial concentrations of anhydride and alcohol, respectively, and x is the amount of reaction at time t. Only four or five points are taken after the faster reacting alcohol has been esterified (determined from the rate constants or a previous analysis). The concentration of the faster reacting alcohol is found by extrapolation of the line through the points to zero time. Let $a = a_1 + a_2$, where a_1

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is the concentration of the more reactive hydroxyl. At the intercept where t = 0, x = a_1 and $\log \frac{(b - x)}{(a - x)} = \log \frac{(b - a_1)}{(a - a_1)}$ = the value at the intercept.

The most practical molar ratio of anhydride to alcohol is 2 to 1. Their concentrations must not be equal because then a = b and the log term will be zero. When more than 70% of the more reactive alcohol is present, add a known amount of the less reactive one and correct the final result for the amount added. For samples containing less than 10% of the more reactive species, it is expedient to use a larger sample and have the hydroxyl in excess of the anhydride. The presence of small amounts of water or aldehydes does not interfere.

Second order rate constants for twelve primary and secondary alcohols were measured at 26°C. These are in the same order as predicted from differences in their steric requirements. On the basis of the ratio of the rate constants (primary to secondary) for acid catalyzed isobutyrylation and base catalyzed acetylation, the former reagent appears to be more sensitive toward steric interactions. An increase in the acid concentration of the isobutyric anhydride reagent increases the rate constant of 2-butanol, as expected, but the increase in rate is not linear.

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INTRODUCTION

Until recently, the literature contained no general chemical method for the analysis of mixtures of alcohols. The method described herein is based on the differences in reaction rates of different alcohols with isobutyric anhydride, using pyridine as solvent and perchloric acid as catalyst.

The method utilizes second order kinetics, wherein the rate of the reaction is dependent upon the concentrations of both reacting species, the alcohol and the anhydride. From a plot of the kinetic data and extrapolation back to zero time, the concentration of the more reactive alcohol is determined directly from the intercept at zero time. Knowing the total concentration of hydroxyl present, the concentration of the less reactive species is determined by difference.

HISTORICAL

Analysis of Mixtures

Few methods for the analysis of mixtures of alcohols have appeared in the literature, even though the basic principles for an analytical method were established approximately ten years ago.

Lee and Kolthoff (1) in 1951 formulated the first method for the analysis of mixtures based on rates of reaction. They realized that the same functional group on different organic molecules often exhibits differences in its rate of reaction with a given reagent. This difference in reaction rate is frequently due to the size and configuration of the molecule to which the functional group is attached. They illustrated that a mixture of two organic compounds containing the same functional group could be analyzed by measuring their rates of reaction with a third substance. The total amount of the two compounds was determined by a fast reaction and then determined the amount reacted with the reagent under rigidly fixed conditions and after a specified optimum time. The optimum reaction time was calculated from values of the specific rate constants. Reference to calibration curves gave the composition of the mixture. While only two measurements are required per analysis, after establishment of the calibration curves, the somewhat long and exacting procedure probably curtailed much investigation

of this method. They also illustrated that the error
decreased as the ratio of the two rate constants increased.

Two methods for the specific determination of 2-propanol
in mixtures involved oxidation of the 2-propanol to acetone
and subsequent determination of the acetone produced.
Etienne (2) determined traces of 2-propanol in various
mixtures by oxidation to acetone with acidic potassium
dichromate. The resulting acetone was then condensed to
difurfurylidene-acetone which had a red or violet color in
acid solution. The absorbence was measured at 425 mu.
Strache and Martienssen (3) analyzed aqueous mixtures of
ethanol and 2-propanol by a direct titration scheme with
chromic acid, utilizing a knowledge of the densities of the
aqueous solutions.

Recently, Critchfield and Hutchinson (4) described a
method for the determination of small amounts of secondary
alcohol in the presence of primary alcohol. Oxidation of
the sample with acidic potassium dichromate formed ketones
from the secondary alcohols. Primary alcohols were oxidized
to carboxylic acids and did not interfere. Hypophosphorous
acid was used to reduce the excess dichromate and the acid
was neutralized before the addition of 2,4-dinitrophenyl-
hydrazine. The ketones generally reacted quantitatively with
the 2,4-dinitrophenylhydrazine in less than 30 minutes. The
absorbence was measured at 480 mu. A separate calibration

curve had to be obtained for each secondary alcohol deter-
mined. The oxidation time varied from 5 to 120 minutes,
depending upon the alcohols oxidized. The method was not
applicable for the determination of cyclic secondary alcohols
or highly branched aliphatic alcohols because these compounds
were oxidized to acids.

In 1961, Siggia and Hanna (5) presented a general method
of analysis which utilized second order reaction rates to
analyze mixtures of alcohols. Their method was based on the
differences in reaction rates of different alcohols with
acetic anhydride in pyridine. The second order reaction data
were plotted in the conventional manner. Ten-ml. aliquots
were removed, at intervals, from the reaction mixture (50
millimoles of hydroxyl and 10 ml. of acetic anhydride per 250
ml. solution), hydrolyzed, and titrated with standard base.
A blank was run similarly. Then $\log \frac{(b - x)}{(a - x)}$ was plotted
versus time, where x was the decrease in concentration of
reactant in time t, and a and b were the initial concentra-
tions of alcohol and anhydride, respectively. A mixture was
indicated when a curve with two straight-line portions was
observed. The upper line representing the slope of the less
reactive alcohol was extrapolated to point A at zero time
(Figure 1). A line AB was drawn parallel to the time axis
and the time T, at point B of the intersection between this
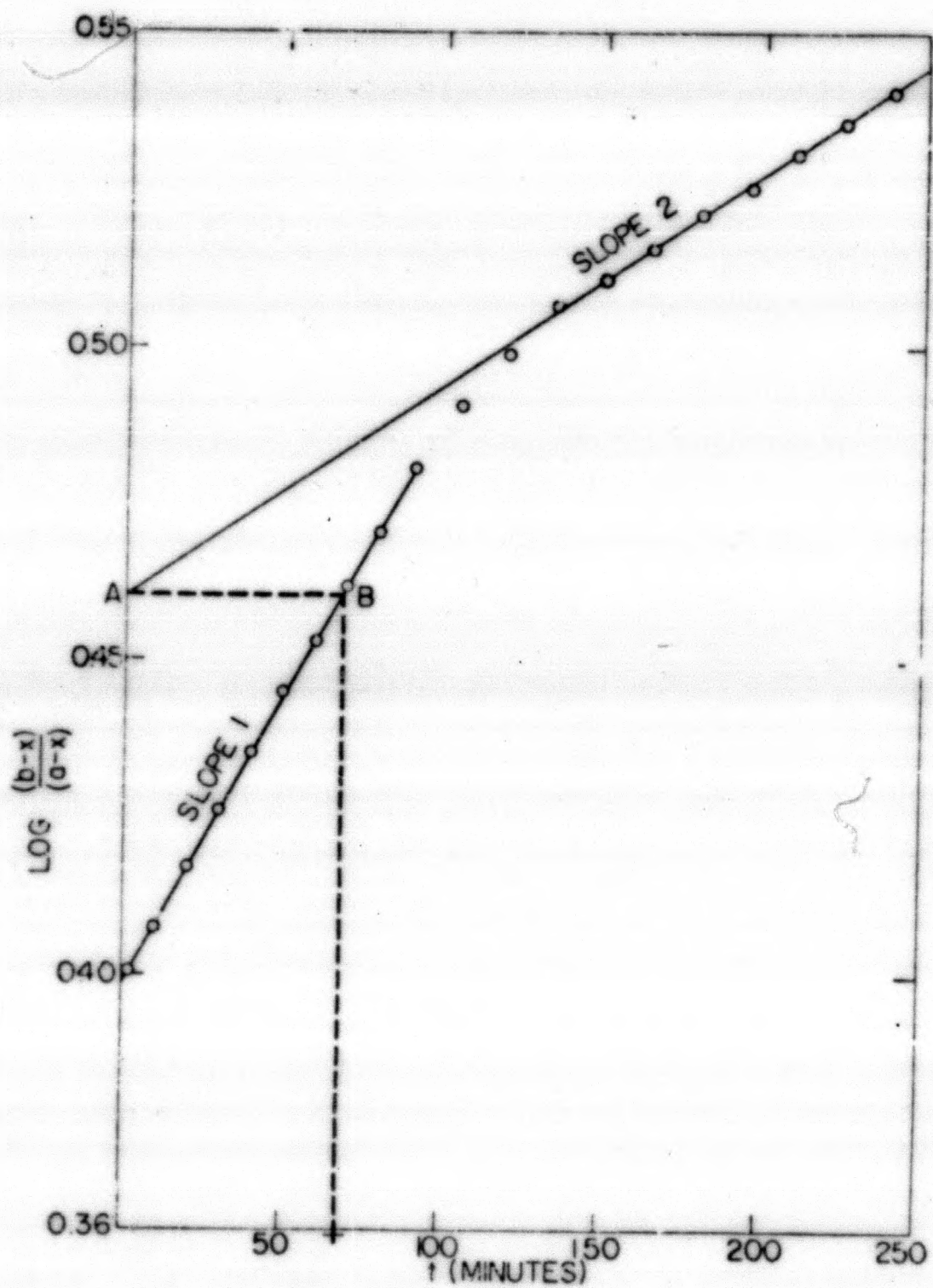line and the lower slope, was read. The concentration of

Figure 1. Plot for analysis of a mixture of alcohols via method of Siggia and Hanna (5)

the more reactive alcohol is then the concentration of
alcohol reacted at this time. The concentration was then
determined by a plot of x versus t. The total hydroxyl
content of the sample was determined by an established
acetylation procedure. All of the reactions were followed
for approximately 300 minutes.

Base-Catalyzed Acylations

Gold and Jefferson (6) have proposed a mechanism for
pyridine-catalyzed hydrolysis of acetic anhydride:

$$C_5H_5N + Ac_2O \rightleftharpoons C_5H_5NAc^+, OAc^- \tag{1}$$

$$C_5H_5NAc^+ + H_2O \rightleftharpoons C_5H_5NH^+ + HOAc \tag{2}$$
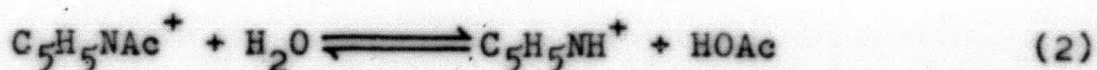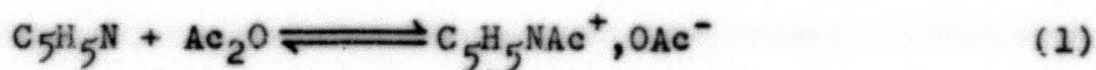
Reaction 1 was rate determining with the hydrolysis of the
pyridine-isobutyrylium ion being rapid in reaction 2.
Pyridine, 3-methylpyridine, and 4-methylpyridine all
catalyzed the hydrolysis rapidly while steric hindrance in
the case of 2-methylpyridine or 2,6-dimethylpyridine
inhibited the catalytic effect.

Acid-Catalyzed Acylations

Physical organic studies have established that perchloric
acid forms a very reactive acetylium ion which is then capable
of acetylating any hydroxyl group rapidly. Gillespie (7) has
demonstrated the presence of the acetylium ion by cryoscopic
measurements of acetic anhydride in excess sulfuric acid.

Burton and Praill (8) have established that perchloric acid is more effective than sulfuric in the formation of the acetylium ion. Their mechanism involves the formation of a reactive acetylium ion intermediate in equilibrium with acetic anhydride:

$$Ac_2O + H^+ \rightleftharpoons Ac_2OH^+ \rightleftharpoons Ac^+ + HOAc \tag{3}$$

$$Ac^+ + ROH \rightleftharpoons ROAc + H^+ \tag{4}$$
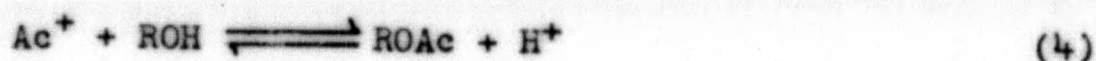
The equilibrium is shifted to the right by the reaction of any electrophile such as an alcohol with the acetylium ion. The regenerated proton in reaction 4 can rapidly reestablish the equilibrium.

Mechanism of the Reaction

The mechanistic hydrolysis of the pyridine-acetylium ion proposed by Gold and Jefferson (6) can be modified for the reaction with alcohols, preceded by acid catalysis to form an equilibrium amount of the pyridine-isobutyrylium ion (which should form nearly as readily as the acetylium ion); letting Byl equal $(CH_3)_2CHCO$:

$$Byl_2O + C_5H_5NH^+ \rightleftharpoons C_5H_5NByl^+ + HOByl \tag{5}$$

$$C_5H_5NByl^+ + ROH \rightleftharpoons C_5H_5NH^+ + ROByl \tag{6}$$
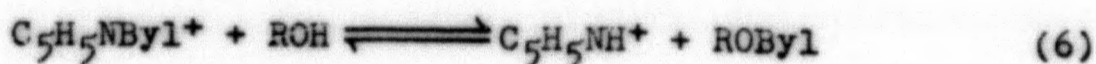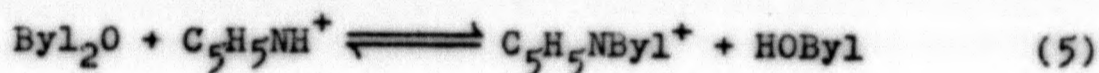
The pyridinium ion should be in equilibrium with a proton and pyridine, and thus catalyze the formation of the

pyridinium-isobutyrylium ion in reaction 5 via the following pathway:

$$C_5H_5NH^+ \rightleftharpoons C_5H_5N + H^+ + Byl_2O \rightleftharpoons Byl_2OH^+ \quad (7)$$

$$Byl_2OH^+ + C_5H_5N \longrightarrow C_5H_5NByl^+ + HOByl \quad (8)$$
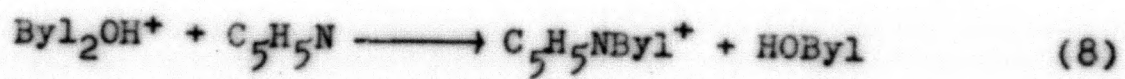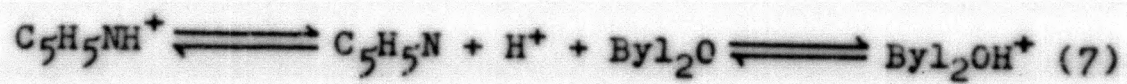
The isobutyric anhydrium ion probably reacts reversibly with the pyridine rather than dissociating into the free isobutyrylium ion. Since reaction 6 is a displacement reaction, it should be subject to steric hindrance.

EXPERIMENTAL

Development of the Method

Preliminary observations

Schenk (9) found that by using pyridine as solvent, the acid catalyzed acetylation of various primary and secondary alcohols was complete in 5 and 10 to 60 minutes, respectively. This difference in reaction time suggested that a kinetic method for the analysis of mixtures of alcohols might be feasible, especially if the differences in reaction time could be enhanced via a reagent that could sterically interact with the alcohols. This would emphasize the existing structural differences between the alcohol types and lengthen the time of analysis.

A comprehensive study was made of the following anhydrides: propionic, butyric, isobutyric, pivalic, hexahydrobenzoic, benzoic, and p-nitrobenzoic. The aliphatic anhydrides generally reacted too fast in ethyl acetate containing perchloric acid. For example, purities of 90 and 93% were obtained from the analysis of 2,6-diisopropylphenol and benzyl alcohol, respectively, after a five minute reaction with 0.25M hexahydrobenzoic anhydride containing 0.006M acid. The rate of acylation with the aromatic anhydrides in ethyl acetate was decreased as the acid concentration was increased. A purity of 34%

was obtained from 1-butanol after a 10 minute reaction with 0.25M benzoic anhydride containing 0.006M acid but only 18% with an acid concentration of 0.012M. The aromatic anhydrides were hydrolyzed with difficulty in both ethyl acetate and pyridine, often requiring 20 minutes versus 5 minutes for the aliphatic ones.

The rate of reaction was greatly reduced in pyridine. Purities of 0 and 63% were obtained for the analysis of 2,6-diisopropylphenol and benzyl alcohol, respectively, after a 60 minute reaction with 0.25M hexahydrobenzoic anhydride containing 0.02M perchloric acid. Purities of 80 and 31% after 60 minutes and 67 and 19% after 30 minutes were obtained from the analysis of benzyl and isopropyl alcohols, respectively, with 0.25M isobutyric anhydride containing 0.04M acid.

It was predicted that pivalic anhydride would yield the greatest difference between the extent of reaction of primary and secondary alcohols. However, it was extremely difficult to hydrolyze, requiring 20 minutes at 60°C, and also had to be synthesized since it was not readily available.

Selection of reaction order

When a single point method of analysis can not be realized, an attempt is frequently made to perform the analysis by use of kinetics. Reaction order gives the dependence of rate on concentration. The first method

attempted was a pseudo first order reaction, wherein the isobutyric anhydride was present in approximately ten fold excess, as recommended by Fritz and Hammond (10), so that the hydroxyl or alcohol was the only species whose relative concentration changes appreciably throughout the reaction period. Thus the rate of reaction was proportional to the concentration of the alcohol.

The difficulty with this mode of attack was in the means of measuring the amount of reaction or reagent consumed at various intervals of time. An aliquot of the sample was hydrolyzed. The amount of reaction was equal to the difference between the volume of standard base required for the titration of the sample and the volume for the blank. For a typical run, the difference between the blank (45.0 ml.) and the final point was only 1.5 ml., and this had to be spread out over approximately nine points. A plot of the data frequently possessed a "shot gun effect".

An attempt was made to find a reagent that would act as a strong base but a poor nucleophile and thus permit the direct titration of the carboxylic acid formed during the reaction while undergoing only slight interaction with the excess anhydride. This direct titration would greatly enhance the accuracy of the plot. Tetramethylguanidine $(Me_2NC(=NH)NMe_2)$ was tried but attempts at achieving a sharp potentiometric endpoint were unsuccessful.

The next approach was to try second order kinetics wherein the rate of reaction is dependent upon the concentration of both species. Readily obtainable straight lines resulting from the plot of the kinetic data suggested that this method should be applicable to mixtures of alcohols.

Concentration of the anhydride

The limits for the concentration of anhydride are fixed by keeping the 0.11N sodium hydroxide titration of the hydrolyzed blank within 25 ml. and by using a low enough concentration of anhydride to permit use of a 5.0 ml. pipet. This amounts to roughly 0.25M anhydride reagent, allowing for the base consumed by the acid catalyst.

Hydrolysis of isobutyric anhydride (0.0025M acid)

The anhydride hydrolyzes satisfactorily in five minutes at room temperature when accompanied by magnetic stirring. Approximately 98% of the anhydride hydrolyzes during the first minute by this method. To ensure best results it is suggested that a 10 minute period be utilized after the initial mixing of the reagent and water if the solution is not stirred.

Reagents

0.25M isobutyric anhydride (0.0025M acid)

Add 0.05 ml. of 72% perchloric acid to 235 ml. of ACS grade pyridine (previously cooled to 0°C) in a clean,

acetone-free 250 ml. glass stoppered flask, into which is pipetted
10.5 ml. isobutyric anhydride (Eastman practical grade -
fractional distilled). Thoroughly mix and allow the reagent
to come to room temperature, or place the flask in a constant
temperature bath. A yellow coloration will slowly develop
over a period of three to four weeks. However, the color
does not interfere with the end-point, using either
indicator.

0.11N alcoholic sodium hydroxide

To 55 ml. of saturated aqueous sodium hydroxide
(carbonate free), add 125 ml. of carbonate free water and 9
liters of either absolute acetone-free methanol or freshly
opened methyl cellosolve (Union Carbide Chemicals Co.).

Titration indicators

Mix one part of 0.1% neutralized aqueous cresol red .
with three parts of neutralized thymol blue.

For colored solutions, mix 2.5 parts of 0.1% nile-blue
sulfate in 50% ethanol and one part of 1% phenophthalein in
95% ethanol. This frequently yields a more distinct end-
point.

Potassium acid phthalate (primary standard grade)

Procedure

Transfer approximately 48 ml. of the isobutyric
anhydride reagent to a 50 ml. volumetric flask placed in a

constant temperature bath or kept in a room where the
temperature is reasonably constant. Add a weighed sample
containing approximately 5 to 6 millimoles of hydroxyl.
Determine the total hydroxyl content of the sample by the
method of Fritz and Schenk (11). Rapidly fill to the mark
with reagent, note (record) the time and thoroughly
equilibrate the solution. After the faster reacting
component has reacted (determined from their rate constants
or from a previous run), at intervals of time (usually 20 to
30 minutes) pipet a 5.0-ml. aliquot into a 125-ml. glass-
stoppered flask, add 2 to 2.5 ml. water and magnetically stir
the solution for 5 minutes at room temperature or allow it to
stand, after mixing, for 10 minutes. Titrate with the 0.11N
alcoholic sodium hydroxide.

Determine a blank by pipetting 5.0 ml. of the anhydride
reagent into a 125 ml. glass-stoppered flask, hydrolyzing as
above and titrating to the same end-point.

Standardize the approximately 0.11N sodium hydroxide
against dried potassium acid phthalate, using the same end-
point.

Caution: Do not heat any acylating solution containing
perchloric acid; dispose of solutions promptly when the
determination is finished. Heating samples with perchloric
acid present is not recommended. If heating is absolutely
necessary, prepare the acylating reagent with an equivalent

amount of p-toluene sulfonic acid.

Plot log $\frac{(b - x)}{(a - x)}$ versus time, where a and b are the initial concentrations of alcohol and anhydride, respectively, and x is the decrease in concentration of reactant at time t. Extrapolate the line through the points to point D at zero time (Figure 2). Calculate the concentration of the more reactive species from the value of the intercept, point D.

Since the total alcohol concentration, a, is equal to f + s, where f is the concentration of the more reactive alcohol, x = f at t = 0. Hence log $\frac{(b - x)}{(a - x)}$ = log $\frac{(b - f)}{(a - f)}$ = value at D, the intercept. Thus, f = $\frac{(\text{antilog } D)\ a - b}{(\text{antilog } D) - 1}$.

Acylation Samples

The alcohols used as standards were either Reagent Grade or Eastman White Label chemicals. A two microliter sample of each alcohol was run through an F & M Model 500 gas chromatograph, using a 4 ft. column containing 10% Carbowax 20M on Haloport F (fluorocarbon support - reduces tailing of water). Samples containing over 2% impurities (generally lower boiling alcohols) were fractional distilled through a Todd Model A column (20 to 50 theoretical plates). The various mixtures were prepared by weight.

The 3-methyl-2-butanol was prepared via lithium aluminum hydride reduction of the corresponding ketone and subsequently distilled, after normal workup and the addition
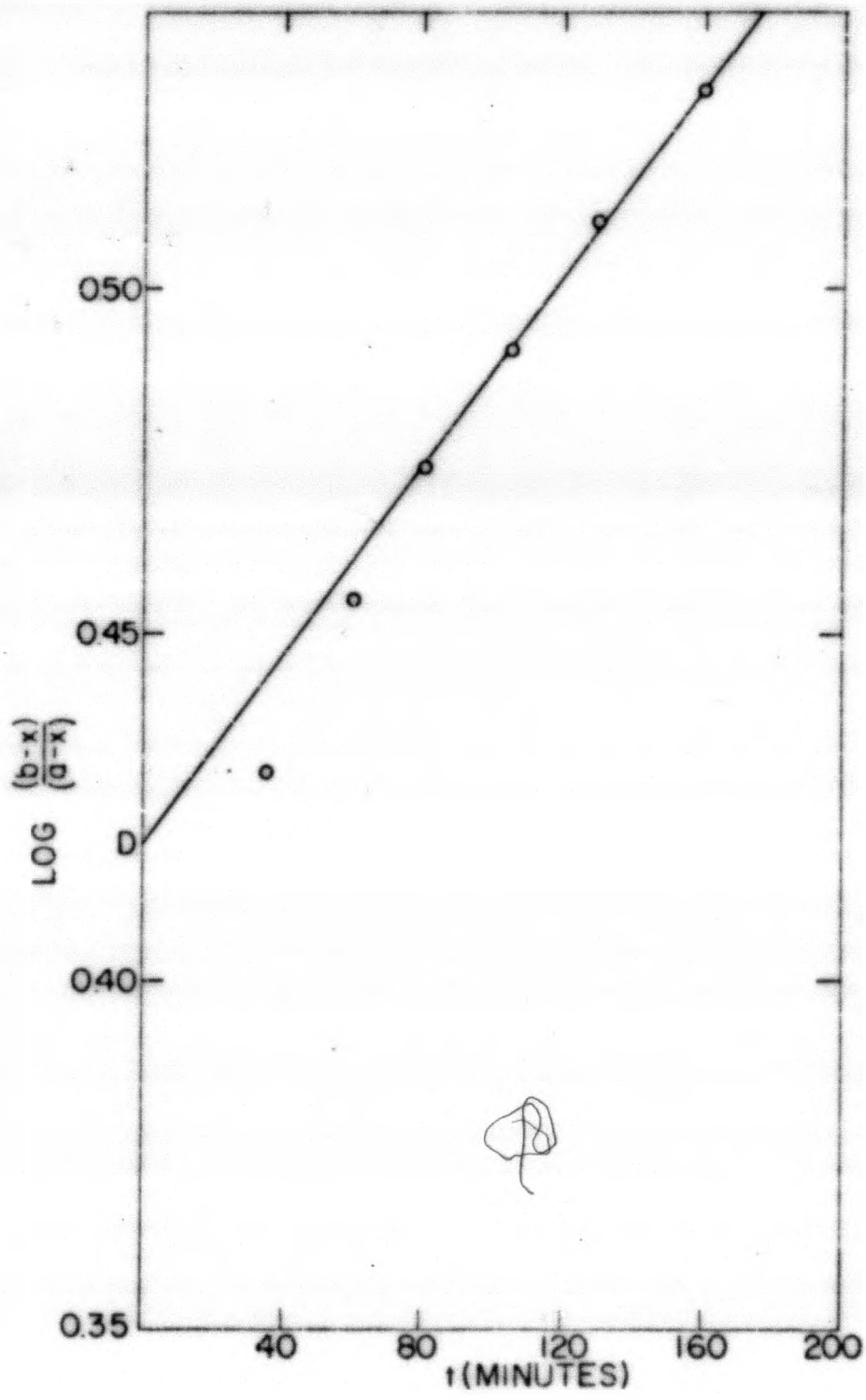
Figure 2. Plot of data from proposed method of analysis

2,4-dinitrophenylhydrazine to remove any unreacted ketone.

Rate Constants

The second order rate constants for the individual alcohols were determined by the same procedure as used for the analysis of the mixtures, except that the first point was taken within the first 10 minutes. The remaining four points were spaced so that there was approximately 0.20 ml. titrant difference between each point. A plot of $\frac{2.303}{b - a} \log \frac{a(b - x)}{b(a - x)}$ versus t yielded the rate constant, which is equal to the slope of the straight line through the points. The reagent and samples were kept at 26°C in a constant temperature bath.

Rate constants were also determined for several alcohols using 0.25M acetic anhydride in pyridine in the absence of acid catalyst.

Effect of Acid Concentration upon Rate Constant

The isobutyric anhydride reagent was prepared with acid concentrations of 0.0013, 0.0025, 0.0050, and 0.010M, by the addition of 0.025 ml., 0.05 ml., 0.10 ml., and 0.20 ml. of 72% perchloric acid, respectively, in order to determine the effect of acid concentration upon the rate of acylation of 2-butanol. The rate constants were determined as above.

RESULTS

Second Order Rate Constants

Table 1 lists second order rate constants for twelve primary and secondary alcohols in 0.25M isobutyric anhydride containing 0.0025M perchloric acid. All of these rates were measured at 26°C. The initial alcohol concentration was kept in the range of 5.5 to 6.0 millimoles per 5.0 ml. of reagent so that there would be better correlation between the values. The rate constants generally fall in the same order that they would be placed from a consideration of the steric interaction between the alcohol and the anhydride.

Table 1. Second order rate constants for alcohols in 0.25M isobutyric anhydride containing 0.0025M perchloric acid at 26°C

Alcohol	k (liters mole^{-1} sec^{-1}) x 10^4
1-Propanol	2.40
2-Propanol	0.413
1-Butanol	2.59
2-Butanol	0.352
2,2-Dimethyl-1-propanol	1.43
3-Methyl-2-butanol	0.181
3-Pentanol	0.268
Cyclopentanol	0.355
Cyclohexanol	0.389
2-Methylcyclohexanol	0.253
2-Phenylcyclohexanol	0.252
Benzyl	1.90

Table 2. Comparison of rate constants in pyridine catalyzed
0.25M acetic anhydride and acid catalyzed 0.25M
isobutyric anhydride

Alcohol	k (liters mole^{-1} sec^{-1}) x 10^4 anhydride	
	acetic	isobutyric (0.0025M acid)
1-Butanol	0.550	2.59
2-Butanol	0.143	0.352
3-Methyl-2-butanol	0.139	0.181
2-Methylcyclohexanol	0.136	0.253

Table 2 lists rate constants for four representative
alcohols, as measured in 0.25M acetic anhydride and in 0.25M
isobutyric anhydride which contains 0.0025M perchloric acid.
This yields a more direct comparison of the two reagents
except that the actual concentration of the acetic anhydride
reagent of Siggia and Hanna (5) is approximately 0.4M. One
advantage of the acid catalyzed reagent is that only 120 to
180 minutes is required for the average mixture while 250 to
300 minutes is required for the uncatalyzed procedure. The
ratio of the rate constants (1-butanol to 2-butanol) for each
reagent clearly implies that the isobutyric anhydride reagent
is more sensitive towards steric hindrance. The three
secondary alcohols show almost the same degree of reactivity
towards the acetic anhydride while there is an appreciable
difference in the case of the isobutyric anhydride.

Table 3. Effect of acid concentration on the rate constant of 2-butanol in isobutyric anhydride

Acid concentration molarity	k (liters mole^{-1} sec^{-1}) x 10^5
0.0013	2.23
0.0025	3.52
0.0050	5.70
0.010	7.41

Certainly, 2-butanol would not offer as much steric inter-action as 3-methyl-2-butanol. This also indicates that the isobutyric reagent has more differentiating power.

The rate constants listed in Table 3 clearly demonstrate the effect of increasing or decreasing the catalyst concentration on the reaction rate of 2-butanol. The values repre-sented the average of at least two separate runs. The rate constants for other alcohols should behave in a similar manner. A higher acid concentration should be beneficial, from a time standpoint, for the analysis of mixtures containing 40 to 90% of an isomeric secondary alcohol.

Mixtures and Polyhydroxyl Alcohols

The data presented in Table 4 illustrate the applicability of the method for the determination of mixtures containing both primary and secondary hydroxyl groups. It is recommended that the analysis be run in duplicate in order to

Table 4. Alcohol mixtures and polyhydroxyl alcohols

Alcohols		Present	% Primary Found	Average
Primary	Secondary			
1-Propanol	2-Propanol	10.0	10.1,10.3	10.2
"	"	15.1	14.9,15.4	15.2
"	"	49.8	50.1,50.5	50.3
1-Butanol	2-Butanol	65.6	65.9,66.3	66.1
"	"	20.2	20.4,20.6	20.5
Benzyl	2-Propanol	23.0	22.5,22.8	22.6
"	"	49.0	49.3,49.8	49.5
"	"	76.1	75.0,75.6	75.3
Neopentanol	3-Pentanol	6.0	6.1, 6.1	6.1
Glycerol		66.7	65.3,65.9	65.6
1,2-Propanediol		50.0	50.5,50.8	50.6

ensure accurate results. The per cent primary recorded in the
table is an average of two runs. It is evident that mixtures
of isomeric and nonisomeric alcohols, as well as polyhydroxyl
compounds, can be successfully analyzed. Glycerol and 1,2-
propanediol contain both primary and secondary hydroxyl
groups but are simply listed under primary alcohol.

DISCUSSION

Rate Constants

In the case of the two isomeric propanols and butanols, the ratio of the rate constants, primary to secondary, is roughly 6 to 1 and 7.5 to 1, respectively. There is no apparent reason why this ratio should not remain nearly the same as one advanced through the homologous series, each time comparing the 1 and 2 isomers.

A comparison of 3-methyl-2-butanol (k = 0.181) and 3-pentanol (k = 0.268) clearly shows the greater steric effect of a secondary alcohol attached to methyl and isopropyl groups than one attached to two ethyl groups. The other pentanol present, 2,2-dimethyl-1-propanol, shows the effect of having three methyl groups on the alpha carbon. Its rate constant (k = 1.43) is much larger than the other pentanols examined but appreciably less than any other primary alcohol investigated.

While the rate constants for 2-butanol, 3-methyl-2-butanol and 2-methylcyclohexanol are nearly equivalent with acetic anhydride, the rate constants for 2-butanol and 2-methylcyclohexanol are 2 and 1.5 times greater, respectively, than that of 3-methyl-2-butanol in reaction with isobutyric containing 0.0025M acid. This indicates a greater resolving ability for the acid catalyzed isobutyrylation.

The rate constants could be used to predict whether a

particular mixture could be successfully analyzed. The lowest ratio of rate constants utilized for an analysis was 5.3 to 1 for the mixture of 2,2-dimethyl-1-propanol and 3-pentanol. The analysis would certainly be less favorable for the case where the ratio is almost one than when it is 10 or 50 to 1, because the closer the two rate constants are, the smaller the difference between the slopes of the two lines. The limiting case would be where only one straight line could be obtained from a mixture.

The increase in the rate constant for 2-butanol as the acid concentration is increased is not surprising. However, the higher the acid concentration, the greater will be the interference due to the presence of aldehydes. Fritz and Hammond (10) state that aldehydes also interfere somewhat with the standard method of acetylation in hot pyridine. Schenk (9) found that aldehydes are the only major inter- ference in the case of acid catalyzed acetylations in pyridine. His reagent contained more than 60 times as much acid so the effect of aldehydes should be considerably less when using the isobutyric anhydride reagent.

Mixtures

Generally, when more than 70% of the more reactive alcohol is present in the mixture, difficulty is experienced in plotting the data. The upper portion of the reaction rate plot levels off as the reaction nears completion and

becomes unreliable. Thus not even four or five reliable points can be obtained to secure a linear plot for the less reactive alcohol.

A method to overcome this involves the addition of a known amount of the less reactive component to the mixture and correction of the final result for the amount added. However, any error made in this measurement will be magnified several fold. For example, suppose that enough secondary alcohol was added to an isomeric mixture which originally contained only 10% secondary to bring the final concentration to 50%. A 0.5% error made in the measurement of the concentration of the slower reacting alcohol in the "new" sample, after correction for the amount added, would amount to an absolute error of 2.5% since the error would be thrown on only the amount of secondary alcohol present in the original sample.

For the analysis of mixtures containing less than 10% of the faster reacting species, it was necessary to use a larger sample size and thus have the total alcohol in excess of the anhydride. The mixture of neopentanol and 3-pentanol in Table 4 was analyzed in this way, with a molar ratio of alcohol to anhydride of 2 to 1. The concentrations of anhydride and alcohol must not be equal since then a = b and the log term will equal zero.

Only five or six points need to be taken for an average

mixture since only points for the slower reacting species are needed. In Siggia's method, at least twice that many points must be taken because the slope of the faster reacting alcohol must also be determined. This results in a great saving of time as well as reagent. Also his method consumes 50 milli-moles of hydroxyl while this method consumes only 6, something to consider when only a small amount of the alcohol is available for analysis. Also, the acid catalyzed method is faster, enabling twice as many analyses, on the average, to be performed. Finally, the rate of the particular analysis can be increased or decreased merely by increasing or decreasing the concentration of perchloric acid.

Minimum Rate Differences Needed for an Analysis

Since it is extremely difficult to calculate the minimum rate differences from second order kinetics, the same analysis as is applied to unimolecular reactions can be utilized for a reaction that is second order with a rate depending upon the concentration of the reagent(R) as well as the alcohol(a):

$$\frac{dx}{dt} = k_a(a - x)(R - x) \tag{9}$$

In the usual case the reagent will be added in sufficient excess (twofold or more) so that the order of magnitude of the concentration of R will not change over the course of the reaction. Therefore, the value of the product $k_a(R)$ can be

treated as approximately constant.

$$A \xrightarrow{k_a} products \qquad (10)$$

$$B \xrightarrow{k_b} products \qquad (11)$$

$$v_A = \frac{dx_a}{dt} = k_a(R)(a - x_a) \qquad (12)$$

$$v_B = \frac{dx_b}{dt} = k_b(R)(b - x_b) \qquad (13)$$

where a and b are the initial concentrations of A and B, respectively.

The integrated equations are as follows:

$$2.3\log \frac{a}{a - x_a} = k_a(R)(t - t_o) = k_a(R)t_r \qquad (14)$$

$$2.3\log \frac{b}{b - x_b} = k_b(R)(t - t_o) = k_b(R)t_r \qquad (15)$$

where t_r is the reaction time, which will always be the same for two constituents of a mixture. These equations give the simple, time-independent relationship:

$$\frac{\log \frac{a}{a - x_a}}{\log \frac{b}{b - x_b}} = \frac{k_a}{k_b} \qquad (16)$$

The results of the calculation of the concentrations of A and B that will remain at various stages in the lifetime of A, the more reactive constituent, are tabulated in Tables 5 and 6 for a 1:1 mixture.

The results in Table 5 illustrate that a 1:1 mixture

of two alcohols whose rates of reaction differ by a factor of 2 is virtually impossible to analyze, providing that the original assumption is correct. There would not be enough of the slower reacting species present, after 98% of A is destroyed, to permit four kinetic points to be taken. The accuracy will increase as the concentration of A decreases since the amount of B remaining, after 98 to 99% reaction of A, will increase.

The results in Table 6 demonstrate that a 1:1 mixture whose rates of reaction differ by a factor of 3 should be possible to analyze, because after 99% of A has reacted, there is still 22% of B remaining for the establishment of four good kinetic points. As above, the accuracy of the analysis will increase as the concentration of A decreases.

Table 5. Rate of destruction of two compounds whose rates of reaction differ by a factor of 2

Time (expressed as a fraction of initial A destroyed)	$\frac{(A)}{(A_o)}$	$\frac{(B)}{(B_o)}$	$\frac{(B)}{(A)}$
0.00	1.00	1.00	1.00
0.10	0.90	0.95	1.05
0.50	0.50	0.71	1.42
0.90	0.10	0.32	3.2
0.95	0.05	0.22	4.4
0.98	0.02	0.14	7.0
0.999	0.001	0.03	30

Table 6. Rate of destruction of two compounds whose rates
          of reaction differ by a factor of 3

Time (expressed as fraction of initial A destroyed)	$\dfrac{(A)}{(A_o)}$	$\dfrac{(B)}{(B_o)}$	$\dfrac{(B)}{(A)}$
0.00	1.00	1.00	1.00
0.10	0.90	0.97	1.08
0.50	0.50	0.79	1.58
0.80	0.20	0.59	2.95
0.90	0.10	0.47	4.7
0.95	0.05	0.37	7.4
0.99	0.01	0.22	22
0.998	0.002	0.13	130

The lower limit for the analysis of a 1:1 mixture appears to
be the case where the rate constants differ by a factor of 3.
The analysis of a mixture containing 10% of A might be
feasible where the rate constants differed only by a factor
of 2. For a mixture containing 60% or more of A, a factor of
3 would not be sufficient and should be at least 4 or
greater, depending upon the accuracy required. Whatever the
rate factor or the per cent composition of the mixture, there
must be a sufficient concentration of B remaining for the
taking of at least 3 kinetic points. The larger the factor
by which the rate constants differ, the greater the potential
accuracy of the method for any composition.

SUMMARY

Second order rate constants were determined for some primary and secondary alcohols. These generally were in the same order as predicted from differences in their steric requirements. On the basis of the ratio of rate constants for acid catalyzed isobutyrylation and base catalyzed acetylation, the former appeared to be more sensitive towards steric interactions.

An increase in the acid concentration of the isobutyric anhydride increased the rate constant of 2-butanol as expected. The increase in rate was not linear with the increase in catalyst concentration.

The addition of a known amount of the slower reacting alcohol and correction of the final result for the amount added was recommended for analysis of mixtures containing more than 70% of the faster reacting alcohol. For mixtures containing less than 10% of the faster reacting species, it was expedient to use a larger sample size and have the alcohol (total) in excess of the anhydride.

Because of the simplicity of plotting, smaller number of points necessary, smaller sample size and mathematical nature of the calculation coupled with the flexibility of the isobutyrylation method owing to variation of reaction rate with catalyst concentration, it is apparent that this method has much to offer over that with acetic anhydride.

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APPENDIX

Example of Calculations for Typical Analysis

Table 5 lists data and results from the analysis of an isomeric butanol mixture. Assume that a = 0.5501 mmoles per 5 ml. aliquot, b = 1.2630 mmoles per 5 ml. aliquot, V_B (volume of base required for blank) = 23.52 ml. of sodium hydroxide (N = 0.1074), V_S = volume of base required for sample, and x = $(V_B - V_S)N$.

Table 7. Summary of calculations for typical analysis

Time	V_S	$V_B - V_S$	x	b - x	a - x	$\frac{b - x}{a - x}$	$\log\frac{(b-x)}{(a-x)}$
60	21.99	1.53	0.1643	1.0987	0.3858	2.848	0.4545
80	21.75	1.77	0.1901	1.0729	0.3600	2.980	0.4742
105	21.56	1.96	0.2105	1.0525	0.3396	3.099	0.4912
130	21.35	2.17	0.2331	1.0299	0.3170	3.249	0.5118
160	21.19	2.32	0.2492	1.0128	0.2999	3.377	0.5285

For the aliquot removed at 60 minutes, calculate x, which represents either the amount of ester formed or else the amount of anhydride or alcohol consumed, by multiplying 0.1074 (the normality) times 1.53 ml. $\big[V_B(23.52$ ml.$)$ − $V_S(21.99$ ml.$)\big]$. Calculate the terms, b - x and a - x, by subtracting 0.1643 mmoles (x) from 1.2630 mmoles (b) and 0.5501 mmoles (a), respectively. Divide 1.0987 (b - x) by 0.3858 (a - x) and then look up the logarithm of the resulting number (2.848).

Calculate the values for each term at 80, 105, 130 and 160 minutes, similarly. Plot the values for log $\frac{(b - x)}{(a - x)}$ versus their corresponding times. Extrapolate the line through the points to zero time or point D (0.421) on Figure 2. Calculate the concentration of the faster reacting alcohol (f) as follows:

$$f = \frac{(\text{antilog D}) a - b}{(\text{antilog D}) - 1} = \frac{(2.636)\ 0.5501 - 1.2630}{2.636 - 1}$$

$$= 0.1143 \text{ mmoles.}$$

The theoretical value is 0.1112 mmoles.

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END