A MECHANISTIC STUDY OF THE SAPONIFICATION OF PIVALOATE ESTERS

By

Beni Brian Wolf

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ABSTRACT

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The reactions of the esters of trimethyl acetic acid(pivalic acid) have been followed kinetically(Walrath 1977 and Watkins 1986) in the presence of alkali in a 3:1 ethyl cellosolve: water solvent at 64°C. Through the use of both optically active pivaloates and O^{18} as a tracer, the positions of bond fission during saponification for several pivaloates have been determined.

With the secondary butyl ester bimolecular attack on both the acyl- and the alkyl- carbon atom is observed in the presence of alkali. Partial racemization of the product secondary butyl alcohols suggests that for the saponification of secondary butyl pivaloates a combination of the common $B_{ac}2$ saponification mechanism and the rarer $B_{al}2$ mechanism occurs at the above temperature in approximately a 3:1 ratio respectively for the two concurrent reactions. This work provides evidence that both the common $B_{ac}2$ saponification mechanism and the rarer $B_{al}2$ saponification mechanism may occur in a purely aliphatic ester.

In contrast to the secondary butyl ester, O^{18} studies show that the methyl ester undergoes bimolecular attack at only the acyl carbon atom in the presence of alkali. Apparently both the α tertiary butyl group and a secondary alcohol group are necessary to mask nucleophilic attack at the acyl carbon atom. The absence of a secondary alkyl group in methyl pivaloate allows nucleophilic attack at the acyl carbon to occur quite readily.

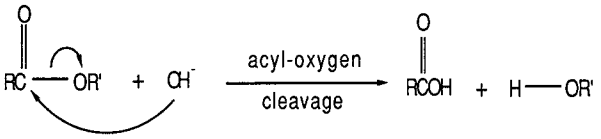
Solvolysis experiments employing phenoxide ion($\Phi O-$) are under way to investigate the effect of the attacking nucleophile's size on the reaction mechanism. Experiments employing O^{18} as a tracer for the saponification of ethyl-, n-butyl-, and secondary butyl pivaloate will begin shortly. This work should provide a more quantitiative measure of the relative extent of each mechanism that occurs during the saponification of secondary butyl pivaloate and should provide insight into the effect of varying alkyl substituents on the mechanism of saponification of pivaloate esters.

1. INTRODUCTION

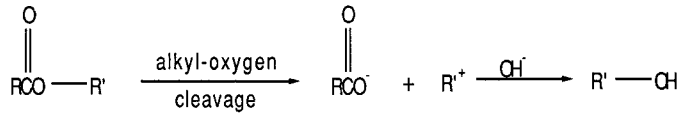
Ester saponification mechanisms have been extensively studied in numerous laboratories. Several mechanisms of ester saponification have been observed and characterized as a result of these studies.[1-4] Ingold has classified these mechanisms as follows[2]:

Table . Ingold Saponification Mechanism Classifications

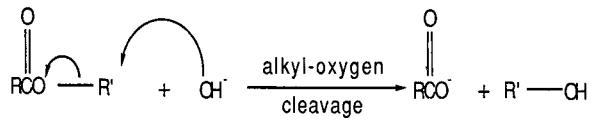
1. $B_{ac}2$ Mechanism = base catalyzed hydrolysis, acyl-oxygen cleavage, bimolecular kinetics



2. $B_{al}1$ Mechanism = base catalyzed hydrolysis, alkyl-oxygen cleavage, umimolecular kinetics



3. $B_{al}2$ Mechanism = base catalyzed hydrolysis, alkyl-oxygen cleavage, bimolecular kinetics



Clearly, the hydrolysis of carboxylic esters may proceed in number of different manners. The actual rate and mechanism of saponification depends largely on the pH of the hydrolyzing solution and the structure of the ester itself.[1-4]

The $B_{ac}2$ mechanism proceeds through a negatively charged

tetrahedral intermediate, followed by release of the alcohol in its unprotonated form. The reaction is in principle reversible, however, a final proton transfer from the carboxylic acid to the alkoxide anion makes the reaction essentially irreversible. This mechanism has an overall second order rate law, first order in both hydroxide ion and ester. Evidence of acyl-oxygen cleavage comes from two separate experiments. First, saponification of optically active esters proceeds with complete retention of configuration in the product alcohol.[5] Second, saponification of esters with heavy oxygen water (H_2O^{18}/ $O^{18}H^-$) results in incorporation of O^{18} only into the resultant acid.[6] Under most conditions, the polar, planar nature of the ester's carbonyl group provides for quick and easy attack by hydroxide ion. Thus, the $B_{ac}2$ mechanism is the dominant saponification mechanism of unhindered aliphatic esters. Its occurrence is so common that it may be considered the "normal" mode of carboxylic ester saponification.[1-4]

At near neutral pH, saponification rates decrease because the hydrolyzing nucleophile switches from OH^- to the weaker nucleophile H_2O. Saponification rate eventually becomes so slow that it falls below the rate of ester ionization. At this point, the $B_{al}1$ mechanism becomes the dominant saponification mechanism. The rate of $B_{al}1$ saponification is dependent only on the concentration of the ester and thus has an overall first order rate law. The ionization of the ester provides evidence for alkyl-oxygen cleavage because saponification of optically active esters results in racemization of the product

alcohol and saponification of allylic esters results in rearrangement to form the most stable product alcohol. [7,8]

The $B_{al}2$ saponification mechanism also involves alkyl-oxygen cleavage; however, the mechanism involves neither ionization of the ester nor unimolecular kinetics. This mechanism is characterized by bimolecular kinetics and a "backside" attack of hydroxide ion at the alkyl carbon of the ester rather than attack at the carbonyl group. Cowdrey *et al* observed that for the saponification of β lactones, the $B_{ac}2$ mechanism is dominant in concentrated alkali; however, under slightly basic conditions β lactones are saponified via the $B_{al}2$ mechanism. Evidence for the $B_{al}2$ mechanism stems both from the second order kinetics and the inversion of configuration observed in the product alcohol when optically active esters were saponified.[9] Bunton *et al* also provided evidence for the "backside" attack of nucleophiles on the alkyl carbon by reacting sodium methoxide with the esters of 2,4,6-triphenyl benzoic acid. The production of a high yield of dimethyl ether and the observation of second order kinetics indicated that a $B_{al}2$ type of mechanism had occurred.[10] Thus, the $B_{al}2$ mechanism has only been observed under special circumstances: relief of ring strain facilitates any attack at alkyl carbon in the β lactone system and the powerful steric hindrance of the *o*-phenyl groups in 2,4,6-triphenyl benzoates prevents attack at the acyl carbon.

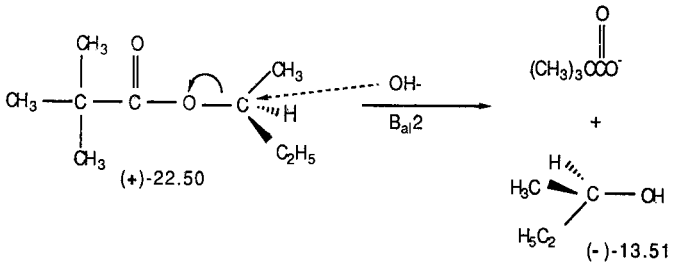
Although the $B_{al}2$ mechanism has been observed in the β lactone

system and for the attack of methoxide ion on 2,4,6-triphenyl benzoates, this mechanism has not been demonstrated for the saponification of a purely aliphatic ester. We have studied the esters of trimethyl acetic acid(pivalic acid) in an effort to observe the $B_{al}2$ mechanism in a purely aliphatic ester. Pivaloate esters were chosen for this study because the tertiary butyl group in the α position provides powerful steric hindrance about the carbonyl group and thus increases the likelihood of attack at the alkyl carbon.

In order to conclusively establish evidence for the $B_{al}2$ mechanism, both bimolecular saponification kinetics and alkyl-oxygen cleavage must be demonstrated. Walrath and Watkins have previously established the kinetics of saponification of pivaloates as second order. [11,12] Therefore, our work has been focused on demonstrating that alkyl-oxygen fission is indeed involved in the saponification of pivaloate esters. We have studied the position of bond fission in two manners. First, by saponifying optically active secondary butyl pivaloate and observing the rotation of the resultant secondary butyl alcohol. Saponification solely by the $B_{al}2$ mechanism would result in alkyl-oxygen fission and complete inversion of configuration in the product alcohol.(see Reactions 1 and 2 on next page) Reaction two, however, indicates that if secondary butyl pivaloate is saponified solely by the $B_{ac}2$ mechanism, the product alcohol retains the same configuration of the ester.

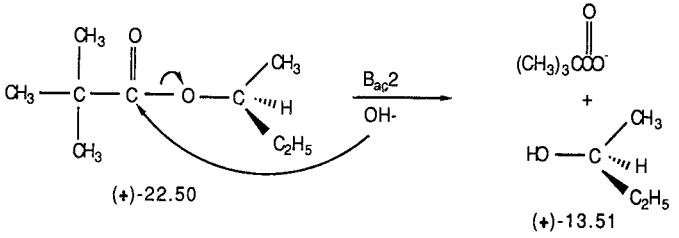
Reaction 1: Theoretical $B_{al}2$ Saponification of Secondary Butyl Pivaloate

1. $B_{al}2$ Mechanism



Reaction 2: Theoretical $B_{ac}2$ Saponification of Secondary Butyl Pivaloate

2. $B_{ac}2$ Mechanism



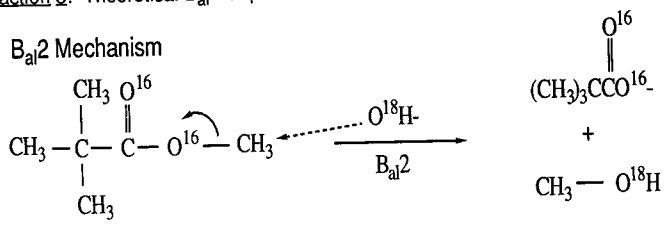
If saponification of the optically active secondary butyl pivaloate involved ester ionization, as in the $B_{al}1$ mechanism, the product alcohol would be optically inactive(racemic).

We have also followed the position of bond cleavage by saponifying methyl pivaloate with heavy oxygen water(H_2O^{18}, $O^{18}H^-$ in reactions 3 and 4

below) and following the incorporation of O^{18} into saponification products by the use of a gas chromatograph-mass spectrometer. Reaction 3 indicates that O^{18}

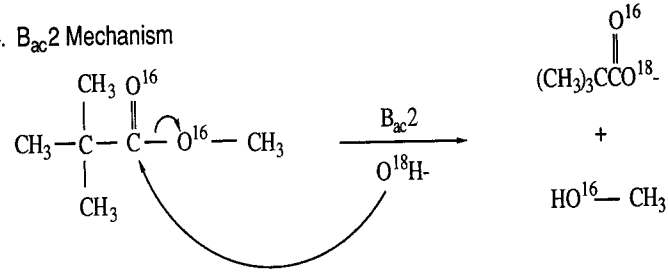
Reaction 3: Theoretical $B_{al}2$ Saponification of Methyl Pivaloate

3. $B_{al}2$ Mechanism



Reaction 4: Theoretical $B_{ac}2$ saponification of Methyl Pivaloate

4. $B_{ac}2$ Mechanism



is incorporated only into the product alcohol during the $B_{al}2$ mechanism. On the other hand, reaction 4 demonstrates that O^{18} is incorporated only into pivalic acid during $B_{ac}2$ saponification. Thus, by comparing mass spectra of heavy water saponification products to ones run with $O^{16}H^-$, it should become possible

to assign relative percentages of O^{18} incorporated into each component of the mixture. This data will allow a conclusion to be drawn as to which mechanism, or relative percentage of each mechanism, that occurs during the saponification process.

2. EXPERIMENTAL

Preparation of Materials.---- Methyl, secondary butyl, and optically active secondary butyl pivaloate were prepared and purified according to the method of V.A. Bochkova *et al.*[12] The optically active secondary butyl alcohols used to prepare optically active secondary butyl pivaloates were supplied by Norse Laboratories Incorporated. Specific rotations(given later) were measured both for the reactant alcohols and purified ester products.

The sodium phenoxide employed in solvolysis reactions was prepared by reacting equimolar amounts of sodium metal with methanol in dimethoxy ethane. Once the reactions were completed, 1ml of water was added to the reaction mixture to increase the solubility of the salts. The initial concentration of the methoxide ion was 0.2M.

Heavy oxygen enriched hydroxide ion, $O^{18}H^-$, was prepared from H_2O^{18} by reacting heavy oxygen water with sodium metal under an $N_2(g)$ atmosphere. The sodium metal employed was cleaned of all O^{16} oxides under an $N_2(g)$ atmosphere prior to reaction. The O^{18} enriched water employed in the isotopic labeling experiments was purchased from Merk and Co., order number

MO 1670. The purity of this reagent was 97 atom % O^{18}.

Solvents.----Solvent choice was dictated by solubility requirements. The ethyl cellosolve solvent used for optically active saponification runs was determined to be >95% pure by vapor phase chromatography. 75% aqueous ethyl cellosolve was prepared by adding 1 part water to 3 parts pure ethyl cellosolve.

The aqueous methanol solvent used for the methanolysis reaction was prepared by adding 5 volumes of water to 95 volumes anhydrous methanol. The dimethoxymethane(DME) solvent employed in the reaction of phenoxide ion with methyl pivaloate, was determined to be greater than 95% pure by vapor phase chromatography. Following formation of phenoxide ion, 1ml of deionized water was added to this solvent to enhance the miscibility of the phenoxide salts with the organic solvent.

The DME solvent employed in the O^{18} saponification runs was dried over several grams of anhydrous $MgSO_4$ for twenty four hours. Following removal of the $MgSO_4$, the DME solvent was again dried over aluminum silicate Molecular Sieves, 4 Angstrom size. Before the O^{18} saponification run, this solvent was distilled to remove any dissolved solids and organic impurities. Throughout the dehydration process, flasks were blown clean with $N_2(g)$ and subsequently stored with $N_2(g)$ above the solutions.

Kinetic Measurements.----Walrath and Watkins have previously established the kinetics of saponification of methyl, secondary butyl, and tertiary

pivaloates as second order at 33°,43°, and 53° C. [9,10]

Saponification of Optically Active Secondary Butyl Pivaloates.----Two saponification runs were performed on optically active secondary butyl pivaloates. Optically active esters were prepared as described earlier. Run 1 employed secondary butyl alcohol of specific rotation, $[\alpha]_{25}$ = -12.51 to synthesize optically active secondary butyl pivaloate, $[\alpha]_{25}$ = -2 ..19. A 3:1 ethyl cellosolve: water solvent was employed for the saponification with an initial ester concentration of 2.5M and an initial base(KOH) concentration of 4.7M. All reactants and the solvent were placed in a glass ampule that was subsequently sealed shut before reaction. (A magnetic stirring rod was placed in the reaction ampule prior to sealing.) The reaction ampule was then placed in a methanol bath under reflux(64° C.). The reaction mixture consisted of two phases: a small. yellow-tinted aqueous phase containing some undissolved solid, beneath a clear, colorless organic phase. Vapor phase chromatography analysis revealed that saponification had gone to completion in one week.(No ester peak at all was observed in the product mixture's chromatogram.)

Run 2 employed optically active secondary butyl pivaloate of specific rotation $[\alpha]_{25}$ = +22.50 that was synthesized from (+)-secondary butyl alcohol($[\alpha]_{25}$ = +12.62) as described earlier. The same saponification apparatus and analyses were used for this run; however, the initial reaction began with 1.7M KOH and 0.90M ester. Vapor phase chromatography analysis

indicated that saponification had gone to completion in one week. (No ester peak at all was observed in the product mixture's chromatogram.)

Kenyon *et al* observed a change in the sign of optical rotation in α,γ-dimethyl allyl alcohols in two months time.[6] To ensure that a change in optical rotation did not occur in secondary butyl alcohol due to reaction conditions, a control experiment was performed under the same saponification conditions as the optically active saponification runs. (-)-Secondary butyl alcohol(0.014mol, ~1M), $[\alpha]$ = -10.51 was placed in a sealed tube containing 1M KOH at 76° and its rotation was followed as a function of time. In addition, the reaction mixture was checked for the presence of any elimination products by gas chromatography.

Analysis of the Optically Active Saponification Runs.----A quantitative mixture of secondary butyl pivaloate, secondary butyl alcohol, and ethyl cellosolve was synthesized and subsequently employed as a standard for the calculation of detector response factors in a Perkin Elmer model 8320 capillary gas chromatograph. Once response factors are calculated, the instrument will normalize data such that the area% values of peak areas correspond directly to mole% values of each component in the mixture. Thus, the extent of saponification can be calculated by employing this instrument to calculate the relative mole percents of secondary butyl alcohol and secondary butyl pivaloate in saponification product mixtures. Saponification runs were allowed to proceed until no ester at all was detected by gas chromatography. Thus, any

rotation observed in the product mixture would be due solely to the resultant secondary butyl alcohol. Solids (glass etchings, KOH, and pivaloate salts)were then removed from the product mixture by distilling off volatile products(secondary butyl alcohol, ethyl cellosolve). Subsequently, a rotation of the distillate was taken in a Rudolph Research Autopol polarimeter. Using the mole% composition data obtained from the gas chromatography analysis, specific rotations were calculated for the product alcohols.

Solvolysis Reactions.----In an effort to qualitatively demonstrate the S_N2-like attack of nucleophiles on the alkyl carbon, solvolysis reactions were performed with alkoxide ions on methyl pivaloate. The formation of an ether from the alkoxide ion and the alcohol moiety of the ester would confirm the backside attack. Methyl pivaloate(0.12M) was reacted with 0.13M KOH in 95% aqueous methanol. In addition to attack by hydroxide ion, some methanolysis was also expected to occur because of the following ion formation: MeOH + OH- <----------> MeO- + H_2O. Although this reaction has an equilibrium that lies far to the left, formation of dimethyl ether(via the $B_{al}2$ attack) would be expected to drive the reaction to the right. Following 40 days of reaction the product mixture was checked for indication of ether formation by gas chromatograph mass spectroscopy(Perkin Elmer model 5992).

A second set of solvolysis reactions studied was the reaction of methyl pivaloate with sodium phenoxide. The sodium phenoxide was made as described earlier. Initial reactant concentrations were as follows: 0.21M

sodium phenoxide, 0.21M methyl pivaloate. Reactions were again performed in sealed glass ampules. Two runs were studied, one at 120° C. and the other at 64° C. Formation of anisole would indicate that backside attack by the phenoxide ion had occurred. Following reaction for 40 days, anisole presence was checked for by gas chromatograph mass spectroscopy.(Perkin Elmer Model 5992)

O^{18} Tracer Studies.---- In all tracer studies the water was isotopically enriched, and the ester was initially of normal abundance. The DME solvent employed in the O^{18} tracer studies was dried as described earlier. DME rather than ethyl cellosolve/water was employed as a solvent in the O^{18} experiments to assure that no transesterification occurred by solvolysis with ethyl cellosolve anion. The methyl pivaloates employed in the saponification were dried in the same manner as the DME solvent. The sodium metal used in the saponification was cleaned of all oxides and hydroxides while under a N_2(g) atmosphere. All glassware used to prepare the reaction mixture was cleared of H_2O^{16} by drying overnight at 150° C. All reagents were weighed, and the actual saponification reaction mixtures prepared, while under a N_2(g) atmosphere in an I^2R glove bag. As in the optically active pivaloate runs, all reactions were performed in sealed glass ampules.

Two O^{18} saponification runs were set up. In Run A, 0.44g(0.022mol) of H_2O^{18} was reacted with 0.21g(0.0091mol) Na(s) to prepare $NaO^{18}H$(aq). Following formation of the hydroxide, 0.92g(0.0079mol) of methyl pivaloate was

added to the reaction mixture. The remaining unreacted water and 6.0ml of DME served as the solvent for the reaction mixture. Assuming that the two phases were completely miscible gives a final ester concentration of 1.1M and a final $NaO^{18}H$ concentration of 1.2M.

In Run B, 0.43g(0.022mol) of H_2O^{18} was reacted with 0.21g(0.0091mol) Na(s) to prepare $NaO^{18}H$(aq). Following formation of the hydroxide, 0.75g(0.0064mol) of methyl pivaloate was added to the reaction mixture. Once again, the remaining, unreacted water and 6.0ml of DME served as the solvent for the reaction mixture. Assuming that the two phases were completely miscible gives a final ester concentration of 0.87M and a final $NaO^{18}H$ concentration of 1.2M. Both reaction mixtures were clear and colorless, with white, undissolved solids(presumably $NaO^{18}H$) at the bottom of the reaction ampules. Reaction temperature was kept constant at 64° C.

A small sample of H_2O^{18} was saved for GC-MS analysis and subsequent determination of atom% O^{18}.

In addition to the two O^{18} runs, an O^{16} control saponification run was also set up. This run had the following conditions: 1.2M $NaO^{16}H$, 1.1M methyl pivaloate in an H_2O^{16}/DME solvent(as before). This reaction mixture was also clear and colorless, with white, undissolved solids at the bottom of the reaction ampule. Reaction temperature was kept constant at 64° C.

When the O^{16} run was heated to 64° C., all undissolved solids went into solution; however, undissolved solids remained at the bottom of the O^{18}

reaction ampules when to 64° C. Apparently, the heavy salt ($NaO^{18}H$), is not as soluble as the O^{16} salt at the same concentration and temperature.

Analysis of O^{18} Saponification Runs.----Extent of saponification was determined by vapor phase chromatography, as with the optically active saponification runs. The O^{16} control run was followed with time in order to determine when saponification had been completed. Once saponification had been completed, saponification products were analyzed by GC-MS. Mass spectra of heavy oxygen saponification products were then compared with standard O^{16} mass spectra to determine both the extent and site of O^{18} incorporation during saponification.

3. RESULTS

TABLE 1: Saponification of Optically Active Secondary Butyl Pivaloates at 64°C

Saponification Run*	$[\alpha]_{25}$ SecBuPiv initial	Distillate Composition Mole%	Observed Final rotation distillate	$[\alpha]_{25}$ SecBuOH Calculated	Apparent $B_{ac}2/B_{al}2$ Ratio
1	**-22.20**	45%SecBuOH 55%EtCellosolve	-3.00	**-8.37**	5:1
2	**+22.50**	22%SecBuOH 78%EtCellosolve	+1.34	**+7.40**	4:1

*Run 1: temp. = 64°C., solvent = 3:1 Et Celloslolve:water, initially - 2.5M ester, 4.7M base
Run 2: temp. = 64°C., solvent = 3:1 Et Celloslolve:water, initially - 0.90M ester, 1.7M base
The literature valueof $[\alpha]_{25}$ for secondary butyl alcohol is +/-13.51.

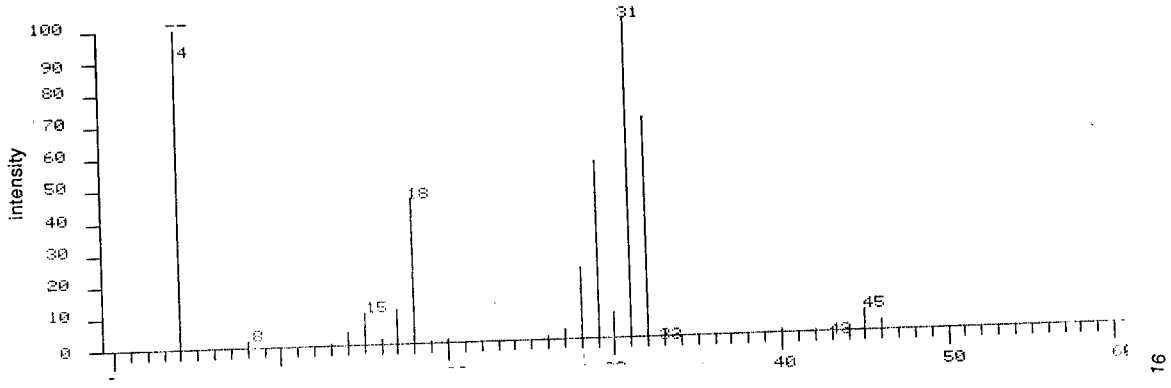
TABLE 2: Control Experiment: Rotation of (-)-SecBuOH in 1M base at 76°C.

Week	Specific Rotation
0	-10.51
2	-9.87
4	-9.50
6	-9.40

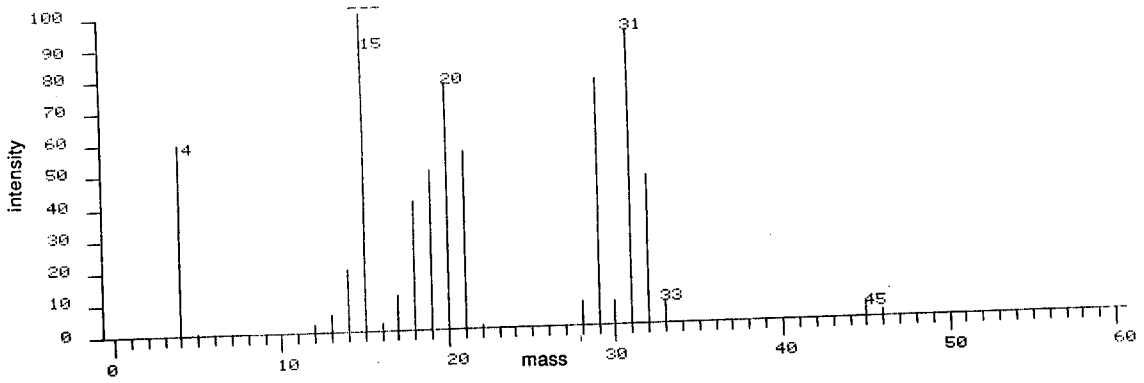
Mass spectra and ion chromatograms for the methyl alcohol saponification product for both the O^{18} saponification run and the control O^{16} saponification of methyl pivaloate are given on the following pages. Mass spectra and mass fragmentation patterns for the following substances are given in the appendix:

1. Methanol
2. Methyl Pivaloate
3. Secondary butyl alcohol
4. Secondary butyl pivaloate
5. Pivalic Acid
6. DME
7. H_2O^{18}(for calculation of atom % O^{18})

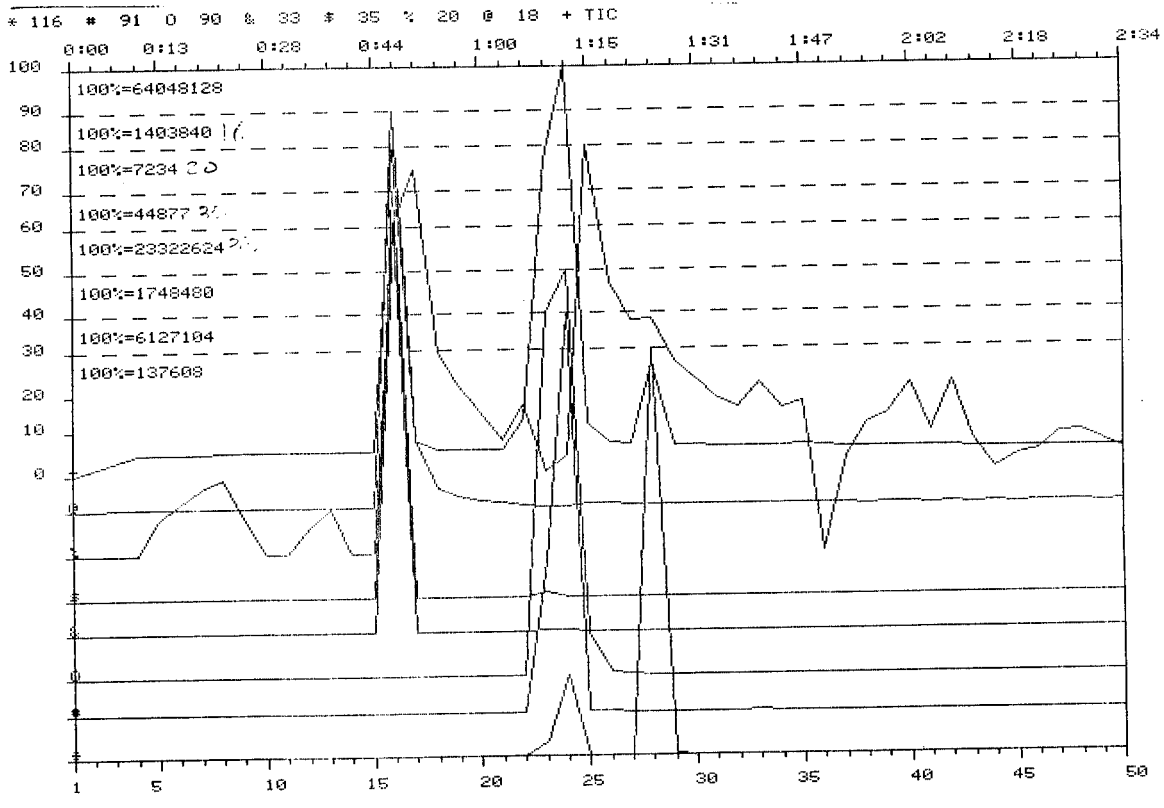
A. METHANOL MASS SPECTRUM: $O^{16}H$- Saponification of Methyl Pivaloate



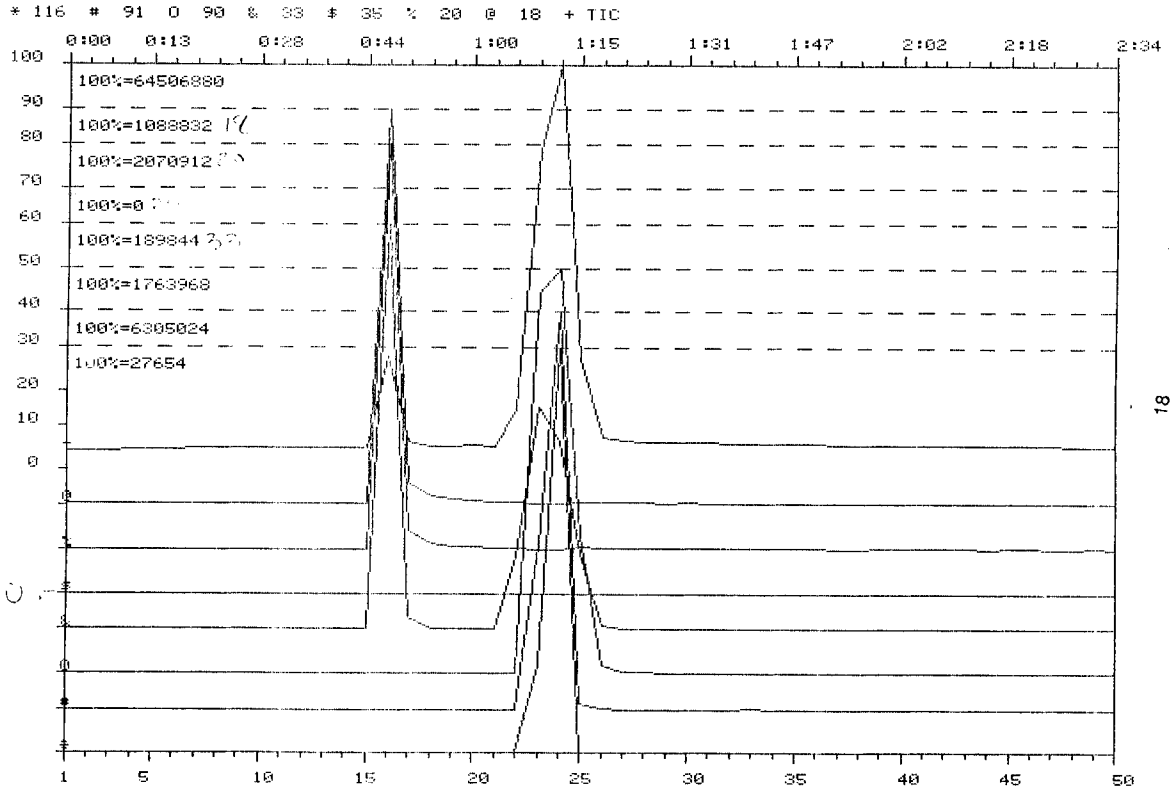
B. METHANOL MASS SPECTRUM: $O^{18}H$- Saponification of Methyl Pivaloate



C. ION CHROMATOGRAM FOR MASS SPECTRUM A: $O^{16}H$- Control



D. ION CHROMATOGRAM FOR MASS SPECTRUM B: $O^{18}H$- Experiment



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4. DISCUSSION

Position of Bond Cleavage.-----In theory, the position of bond fission in ester hydrolysis can be determined unambiguously by saponifying optically active esters and observing the rotation of the resultant alcohol. The inherent characteristics of the three saponification mechanisms allow their differentiation by this method. In the $B_{ac}2$ saponification mechanism, hydroxide ion attacks the acyl carbon and the acyl-oxygen bond is cleaved without changing the configuration of the alcohol moiety. Therefore, the sign of optical rotation in both the ester and product alcohol is the same. In contrast, the characteristic ester ionization observed in the $B_{al}1$ mechanism results in alkyl-oxygen fission with complete racemization of the product alcohol. The $B_{al}2$ mechanism also results in alkyl-oxygen cleavage; however, this mechanism produces a resultant alcohol opposite in rotation sign to the reactant ester. This is due to the S_N2-like attack of hydroxide ion on the alkyl carbon of the ester. Thus, saponification of optically active esters provides insight into the position of bond fission during ester hydrolysis and the actual mechanism of reaction.

Although saponification of optically active esters should provide conclusive information concerning both the position of bond fission and the actual saponification mechanism, this method may lead to misleading data. Kenyon *et al,* for example, observed a change in the sign of optical rotation in α,γ-dimethylallyl alcohol in two months time due to prototropic and anionotropic changes.[7] To ensure that a change in the sign of optical rotation did not occur

in the product secondary butyl alcohols due to reaction conditions, a control experiment following the rotation with time of optically active secondary butyl alcohol was performed under the same saponification conditions as Runs 1 and 2. Table 1 of the results section indicates that (-)-secondary butyl alcohol did not undergo a significant change in rotation in six weeks time under the same saponification conditions as the optically active saponification runs. Further, gas chromatographic analysis of the alcohol at the end of six weeks showed that no elimination products had been formed in six weeks time. Both of these facts ensure that the rotation sign of secondary butyl alcohol was not changed due to saponification conditions. Apparently, the alcohol's rotation is not changed due to anionotropic changes under saponification conditions. Thus, the studies of optically active secondary butyl pivaloates should allow for definitive conclusions to be drawn about the position of bond fission during hydrolysis.

Table 1 of the results section shows that the saponification of two enantiomeric secondary butyl pivaloates, under the same reaction conditions, both produced partially racemized secondary butyl alcohols. The relative proximity of the specific rotation of these product alcohols suggests that same mechanistic process was involved in each run. The racemization observed may indicate that the $B_{al}1$ mechanism has occurred; however, the ester ionization involved in this mechanism is unlikely at this concentration of base. In addition, the $B_{al}1$ mechanism alone could not have occurred because this would have

resulted in complete racemization of the product alcohol. The fact that racemization is involved in the mechanism does however, suggest that some form of alkyl-oxygen fission($B_{al}1$ or $B_{al}2$) occurs during saponification.

Since neither total inversion nor total retention of configuration was observed in the product alcohols after complete saponification, it may be concluded that saponification did not proceed solely through the $B_{ac}2$ mechanism or solely through the $B_{al}2$ mechanism. If saponification had proceeded only by the $B_{ac}2$ mechanism, the specific rotation of the resultant alcohols would have been of the same sign as the reactant ester and of the same magnitude in rotation as the literature value for secondary butyl alcohol(+/-13.51). On the other hand, if saponification had occurred only through the $B_{al}2$ mechanism, the specific rotation of the resultant alcohols would have been of opposite sign as the reactant ester and of the same magnitude in rotation as the literature value for secondary butyl alcohol. The partial racemization observed suggests that a combination of $B_{al}2$ and $B_{ac}2$ mechanisms(acyl-oxygen and alkyl-oxygen bond cleavages) may have occurred in the saponification process. The optically active saponification studies alone cannot be used to determine the exact mechanism of saponification of secondary butyl pivaloate.

A qualitative way to determine if an S_N2-like attack of nucleophiles does in fact occur at the alkyl carbon, is through the study of solvolysis reactions on pivaloates. The formation of an ether from the solvent alkoxide ion and the

alcohol moiety of the ester would confirm the backside attack. To this end, we have reacted methyl pivaloates with both methoxide ion in a 95%aqueous methanol solvent and phenoxide ion(separately) in a DME/H_2O solvent. In the first case, formation of dimethyl ether would provide evidence for the backside attack of methoxide ion on the alkyl carbon. In the second case, formation of anisole would verify that a $B_{al}2$ type of mechanism. Reactions 3 and 4 below demonstrate the simultaneous reactions that are possible in the solvolysis experiments:

Reaction 3: Methanolysis of Methyl pivaloate in 95% aq. methanol at 64° C.*

Acyl-oxygen bond fission:

a) RCO--OMe + OH^- -----> $RCOO^-$ + MeOH
b) RCO--OMe + MeO^- -----> RCOOMe + MeO^-

Alkyl-oxygen bond fission:

c) RCOO--Me + OH^- -----> $RCOO^-$ + MeOH
d) RCOO--Me + MeO^- -----> $RCOO^-$ + MeOMe

*R = tertiary butyl group

Reaction 4: Phenolysis of Methyl pivaloate in DME/H_2O at 64° C. and 120° C.*

Acyl-oxygen bond fission:

e) RCO--OMe + OH^- -----> $RCOO^-$ + MeOH
f) RCO--OMe + ΦO^- -----> RCOOΦ + MeO-

Alkyl-oxygen bond fission:

g) RCOO--Me + OH^- -----> $RCOO^-$ + MeOH
h) RCOO--Me + ΦO^- -----> $RCOO^-$ + MeOΦ

*R = tertiary butyl group
Note: The exact conditions of the solvolysis experiments are given in the experimental section.

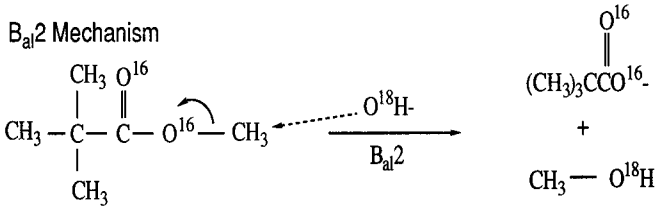
Only reactions (a), (c), and (d) will give identifiable products in the methanolysis experiment, as reaction (b) merely regenerates the methyl ester. The production of dimethyl ether, as in reaction (d) will provide evidence of the

backside attack by methoxide ion at the alkyl carbon. Reactions (e), (f), (g), and (h) will all give identifiable products in the phenolysis reaction. Reactions (e) and (g) will not be distinguishable because each forms the same products. Reaction (f) provides evidence for acyl-oxygen fission by the production of phenyl pivaloate. Only reaction (h) shows that backside attack has occurred at the alkyl carbon. Unfortunately, these experiments have not been completed at the time of writing.

A second, more quantitative way to determine the position of bond fission during hydrolysis, is by the use of heavy oxygen(O^{18}) enriched water ($H_2O^{18}/O^{18}H^-$) as a tracer. This classic method has been used frequently in the determination of ester hydrolysis mechanisms. [5,6] As previously mentioned in the introduction, saponification of methyl pivaloate with $O^{18}H^-$ will lead to O^{18} incorporation into the product alcohol in the $B_{al}2$ mechanism(Reaction 3) or into pivalic acid in the $B_{ac}2$ mechanism (Reaction 4) or into both if a combination of mechanisms occurs. The $B_{al}1$ mechanism would result in O^{18} incorporation in both the alcohol(by hydrolysis) and the acid(by solvent exchange).

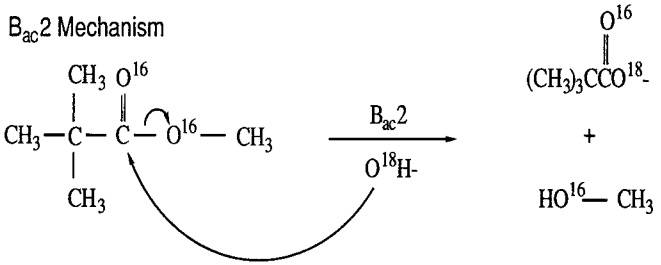
Reaction 3: Theoretical $B_{al}2$ Saponification of Secondary Butyl Pivaloate with $O^{18}H^-$ (see next page)

3. $B_{al}2$ Mechanism



Reaction 4: Theoretical $B_{ac}2$ Saponification of Secondary Butyl Pivaloate with $O^{18}H^-$

4. $B_{ac}2$ Mechanism

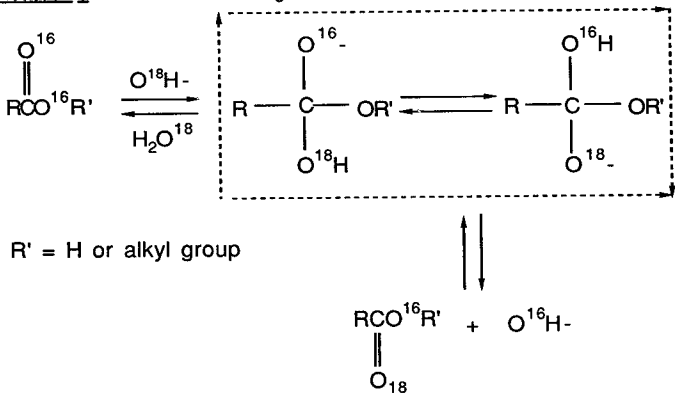


Therefore, it is necessary to establish which mass fragments may be followed in both pivalic acid and methyl alcohol prior to experimentation with $H_2O^{18}/O^{18}H^-$. For this reason, mass spectra were taken for methanol, secondary butyl alcohol (for experimentation with secondary butyl pivaloate), and pivalic acid of normal isotopic abundance.(see appendix for spectra) The peaks which may be followed in these spectra must meet two criteria: 1. They must be large enough so that a change in the amount of isotope formed can be measured quantitatively by the amount of increase or decrease in peak height. 2. They

may not have a significantly sized peak two mass units higher because if O^{18} is incorporated, the subsequent mass fragments will exhibit masses two units higher.

It is also important to note that Bender demonstrated that both esters and carboxylic acids undergo oxygen exchange in aqueous solvents[14]:

Reaction 5: O^{18} Solvent Exchange with Esters and Acids



Therefore, in products of heavy oxygen water saponifications, both pivalic acid and any unreacted ester are expected to contain O^{18} regardless of which mechanism(s) occurs. Thus, our mechanistic analysis with heavy oxygen must focus on the incorporation of O^{18} into the product alcohols(MeOH or Sec BuOH).

Tables 3 through 6, below, summarize the peaks that may be followed in the

product alcohols(based on standard O^{16} spectra(see appendix for spectra). These tables also show hypothesized mass fragments for O^{18} saponification products for both the $B_{al}2$ and $B_{ac}2$ mechanisms.

Table 3: Hypothetical Mass Fragments for Methanol and Pivalic Acid for the $B_{al}2$ Saponification of Methyl Pivaloate with $O^{18}H^-$ *

Methanol O^{16} Mass Fragment	Mass	Hypothesized O^{18} $B_{al}2$ Mass
$CH_3O^{16}H^+$	32	O^{18}=34
CH_3O^{16+}	31	O^{18}=33
Pivalic Acid		**Hypothesized O^{18}**
O^{16} Mass Fragment	**Mass**	**$B_{al}2$ Mass**
Molecular Ion $(CH_3)_3CCOOH^+$	102	102(no O^{18} incorporation)

Table 4: Hypothetical Mass Fragments for Methanol and Pivalic Acid for the $B_{ac}2$ Saponification of Methyl Pivaloate with $O^{18}H^-$ *

Methanol O^{16} Mass Fragment	Mass	Hypothesized O^{18} $B_{ac}2$ Mass
$CH_3O^{16}H^+$	32	32(no O^{18} incorporation)
CH_3O^{16+}	31	31
Pivalic Acid		**Hypothesized O^{18}**
O^{16} Mass Fragment	**Mass**	**$B_{ac}2$ Mass**
Molecular Ion $(CH_3)_3CCOOH^+$	102	104

Table 5: Hypothetical Mass Fragments for Secondary Butyl Alcohol and Pivalic Acid for the $B_{al}2$ Saponification of Secondary Butyl Pivaloate with $O^{18}H^-$

SecBuOH O^{16} Mass Fragment	Mass	Hypothesized O^{18} $B_{al}2$ Mass
Molecular Ion	74	O^{18}=76
M - CH_3	59	O^{18}=61
M - C_2H_5	43	O^{18}=47

Pivalic Acid O^{16} Mass Fragment	Mass	Hypothesized O^{18} $B_{al}2$ Mass
Molecular Ion $(CH_3)_3CCOOH^+$	102	102(no O^{18} incorporation)

Table 6: Hypothetical Mass Fragments for Secondary Butyl Alcohol and Pivalic Acid for the $B_{ac}2$ Saponification of Secondary Butyl Pivaloate

SecBuOH O^{16} Mass Fragment	Mass	Hypothesized O^{18} $B_{ac}2$ Mass
Molecular Ion	74	74(no O^{18} incorporation)
M - CH_3	59	59
M - C_2H_5	43	43

Pivalic Acid O^{16} Mass Fragment	Mass	Hypothesized O^{18} $B_{ac}2$ Mass
Molecular Ion $(CH_3)_3CCOOH^+$	102	104

* Note: the methanol mass spectra given in the results section have different fragmentation patterns because a different instrument was used for analysis. In this case, the standard O16 mass spectra has masses at 33 and 32 rather than at 32 and 31.

Should saponification proceed by both mechanisms as suggested by the optically active saponification runs, both sets of hypothesized peaks would be expected to occur. Their relative heights(mass abundances) compared with standard O^{16} mass fragments, should allow calculation of the relative percent of each mechanism that occurs during saponification. O^{18} experiments have been completed for the saponification of methyl pivaloate and $O^{18}H$- saponification experiments on secondary butyl pivaloate will begin shortly.

Kinetic Form and Mechanism of Reaction. ----In addition to information about the position of bond fission during hydrolysis, data concerning the kinetic form

of the saponification mechanism must be obtained to conclusively establish the reaction mechanism. Walrath and Watkins have separately provided the kinetic data necessary to make mechanistic conclusions regarding the saponification of secondary butyl pivaloate and methyl pivaloate. [11,12] In independent experiments, each has established the kinetics of saponification of methyl-, secondary butyl-, and tertiary butyl-pivaloates as second order at 33°,43°, and 53° C. If it is assumed that these kinetic data are also true for the temperature and concentration of our study(64° C. and @1M base), then it becomes possible to draw conclusions as to the mechanism of saponification.

Since the saponification of secondary butyl pivaloate proceeds with second order kinetics, the $B_{al}1$ mechanism must be ruled out as a possible reaction mechanism due to its characteristic unimolecular kinetics. This mechanism is also unlikely because at a concentration of >1M base, saponification rate should be significantly faster than the ionization rate of the ester. In addition, in the systems in which the $B_{al}1$ mechanism has been reported(allylic and aromatic esters), the carbocations formed(allyl and aromatic cations) would be much more stable than the secondary butyl cation(CH_3-CH_2-CH^+-CH_3) expected to form if the saponification of secondary butyl pivaloate proceeded through the $B_{al}1$ mechanism.m [7,8] These facts all suggest that the $B_{al}1$ mechanism is not involved in the saponification of secondary butyl pivaloate under the conditions of this study.

The partial racemization observed in the optically active secondary butyl

pivaloate studies must be due to a combination of the $B_{ac}2$ and $B_{al}2$ mechanisms since it can not be due to the $B_{al}1$ mechanism. This conclusion is supported by two facts. First, as aforementioned, the $B_{al}1$ mechanism proceeds with unimolecular kinetics which were not observed during this study. Second, if the reaction proceeded through the $B_{al}1$ mechanism, one would expect complete racemization of the product secondary butyl alcohol. Since both the $B_{ac}2$ mechanism and the $B_{al}2$ mechanism both have second order rate laws, if both occurred simultaneously, one would still expect overall second order kinetics: first order in both ester and hydroxide ion. Thus, the competition of the $B_{ac}2$ and $B_{al}2$ mechanisms must be responsible for the partial racemization of secondary butyl alcohol observed in the optically active saponification runs.

The relative extent of $B_{ac}2$ mechanism and $B_{al}2$ mechanism that occurred during optically active saponification runs may be calculated from the specific rotation of the product secondary butyl alcohols and the literature value for the rotation of secondary butyl alcohol. For Run 1, the calculated ratio of $B_{ac}2$ mechanism to $B_{al}2$ mechanism is 4:1(see appendix for sample calculation). The corresponding value for Run 2 is $3B_{ac}2 : 1B_{al}2$. The slight discrepancy between these two values is most probably due to the slight differences in initial saponification conditions. A more precise value of the relative extent of $B_{ac}2$ mechanism and $B_{al}2$ mechanism that occurs during saponification should be available upon completion of the O^{18} tracer studies.

The second order kinetics observed for the saponification of methyl pivaloate suggest that the either the $B_{ac}2$ mechanism or the $B_{al}2$ mechanism or a combination of both is involved in saponification. Mass spectra A and B in the results section show that the product methyl alcohol mass spectra for both the $O^{16}H$- and the $O^{18}H$- saponifications are identical. This fact indicates that only acyl-oxygen cleavage($B_{ac}2$ mechanism) is involved in the saponification of methyl pivaloate. Apparently, both the α tertiary butyl group of pivalic acid and a secondary alkyl group are necessary to observe both mechanisms in a purely aliphatic ester.

Our work illustrates the powerful steric hindrance of the α tertiary butyl group and the secondary butyl alcohol moiety to nucleophilic attack on the acyl carbon atom of secondary butyl pivaloate. This effect occurs to such an extent that the dominant $B_{ac}2$ mechanism is masked enough to observe the slower $B_{al}2$ mechanism. Although both the $B_{ac}2$ mechanism and the $B_{al}2$ mechanism are first order with respect to hydroxide ion, increases in hydroxide ion concentration would be expected to increase the amount of $B_{ac}2$ mechanism that occurs during saponification because this mechanism generally occurs at a faster rate than the $B_{al}2$ mechanism. Our results support this hypothesis: Run 1 initially had an ester concentration of 2.5M and an initial base concentration of 4.7M, resulting in an apparent $B_{ac}2$: $B_{al}2$ ratio of 4:1. On the other hand, Run 2 began with an initial ester concentration of 0.90M and an initial base

concentration of 1.7M and resulted in an apparent $B_{ac}2$:$B_{al}2$ ratio of 3:1. Run 1, the run with higher initial hydroxide ion concentration, resulted in a larger amount of hydrolysis by the $B_{ac}2$ mechanism. This result is in concordance with the postulate that the $B_{ac}2$ mechanism does indeed occur at a faster rate than the $B_{al}2$ mechanism. In theory, the initial concentration of hydroxide ion could be increased to such an extent that saponification by the slower $B_{al}2$ mechanism is almost negligible. Further experimentation could be performed to verify this hypothesis.

Substituent effects have been shown to affect ester hydrolysis mechanisms.[2,3] In the experiment at hand, varying the substituent, R', of pivaloate esters(RCOOR', R = $(CH_3)_3C$-, R' = secondary butyl) should also cause a change in the relative amounts of $B_{ac}2$ and $B_{al}2$ mechanisms that occur during saponification. Since the $B_{ac}2$ mechanism proceeds through a negatively charged intermediate, electron withdrawing substituents on R'(or R) would be expected to increase $B_{ac}2$ reaction velocity, and thus increase the ratio of $B_{ac}2$ to $B_{al}2$ that occurs during saponification. In contrast, placing electron donating substituents on R', would be expected to decrease the rate of $B_{ac}2$ saponification and thus increase the amount of $B_{al}2$ saponification observed. These kinetic effects have been observed in several esters known to undergo saponification through the $B_{ac}2$ mechanism.[2,3]

Although the rate of the $B_{ac}2$ mechanism is particularly susceptible to the

polar effects of substituents, the rate of $B_{al}2$ saponification should not be affected as much by changes in substituent polarity. This is because the $B_{al}2$ mechanism does not proceed through a charged intermediate. However, this S_N2-like nature of the $B_{al}2$ mechanism makes it susceptible to leaving group effects. In the study at hand, the leaving group is the pivalyl anion, $(CH_3)_3CCOO^-$. Any substituent added to the α tertiary butyl group of the pivalyl anion that decreases its basicity should make it a better leaving group and thus increase the amount of $B_{al}2$ observed. These substituents would include electron withdrawing groups that increase the stability of the pivalyl anion.

The S_N2-like nature of the $B_{al}2$ mechanism also makes it susceptible to steric effects. Typically rates of S_N2 reactions are greatest for methyl halides followed by primary alkyl halides, secondary alkyl halides, and tertiary alkyl halides respectively. The energy of the trigonal bipyramidal transition state of S_N2 reactions is increased by steric hindrance. Thus, rates of substitution reactions with tertiary alkyl halides are negligible compared with the rates of methyl halides. Since the $B_{al}2$ mechanism is an S_N2-like reaction, these predictions should also hold for the saponification of pivaloates: Methyl pivaloate would be expected to saponify at a faster rate than n-butyl pivaloate, and n-butyl pivaloate faster than secondary butyl etc. Correspondingly, as the rate of $B_{al}2$ saponification increases, the ratio of $B_{ac}2$ to $B_{al}2$ mechanism that occurs should decrease. We hope to observe this effect in the O^{18}

saponification runs of methyl pivaloate.

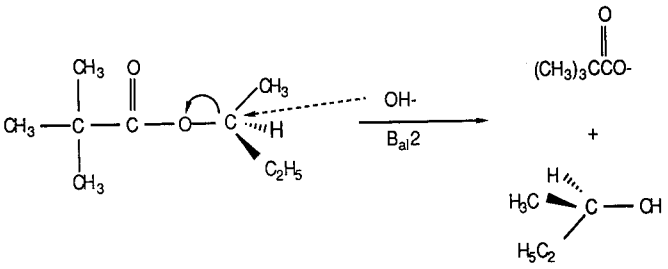
Watkins has provided kinetic data that support the predictions of the preceding paragraph.[12] He demonstrated that pivaloate esters had the following rates of saponification: Methyl- > ethyl- > secondary butyl- >> tertiary butyl-pivaloate. The tertiary butyl ester was not saponified to any significant extent in months at 53° C. Accordingly, the methyl ester would be expected to have the greatest amount of $B_{al}2$ saponification and the tertiary butyl ester the least. A more precise value of the relative extent of $B_{ac}2$ mechanism and $B_{al}2$ mechanism that occurs in each of the pivaloate esters during saponification should be available upon completion of the O^{18} tracer studies.

Ironically the recent results of the saponification of methyl pivaloate with $O^{18}H$- contradict the predictions of the preceding paragraphs. In the methyl ester, only acyl-oxygen cleavage was observed. Apparently, both the α tertiary butyl group of pivalic acid and a secondary alkyl group are necessary to observe both mechanisms in a purely aliphatic ester. Future experimentation with O18 as a tracer during the saponification of ethyl-, n-butyl-, and secondary butyl- pivaloate, as well as the completion of the solvolvysis experiments, will provide more insight into the steric hindrance about the acyl carbon in pivaloate esters.

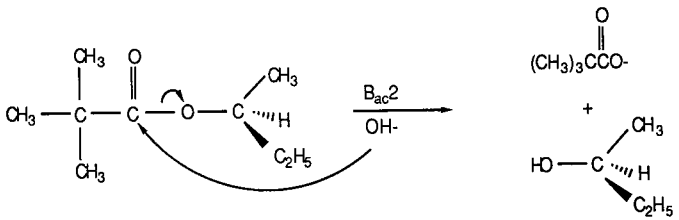
Project Summary.----The saponification of optically active secondary butyl pivaloate illustrates the powerful steric hindrance of the α tertiary butyl group and the secondary alcohol moiety to nucleophilic attack at the acyl carbon. This

work also provides evidence that both the common $B_{ac}2$ saponification mechanism and the rarer, $B_{al}2$ saponification mechanism may occur in a purely aliphatic ester. The two simultaneous reactions are shown below:

1. $B_{al}2$ Mechanism

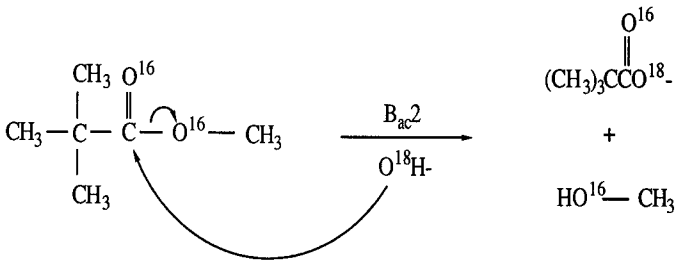


2. $B_{ac}2$ Mechanism



The fact that methyl pivaloate only undergoes saponification by the $B_{ac}2$ mechanism suggests that the secondary alkyl group is necessary to observe

both the $B_{ac}2$ and the $B_{al}2$ mechanisms in a purely aliphatic ester. This reaction is diagrammed below:



Future research will include both the completion of the solvolysis experiments on methyl pivaloate and new O^{18} work on ethyl-, n-butyl-, and secondary butyl pivaloate. This work will provide insight into the effect of varying substituents on the mechanism of saponification and generally increase our knowledge of steric hindrance in the pivaloate ester system.

5. APPENDIX

A. Sample Calculation for Specific Rotation of Resultant Secondary Butyl Alcohol in the Product Mixture of Saponification Run 1

Product Mixture = 1.09g total weight
1.20ml total volume
α observed = -3.00
VPC analysis-->44.5 mol% SecBuOH, 65.5 mol% EtCell

mol% SecBuOH = mol fraction SecBuOH in the product mixture
mol fraction SecBuOH = moles SecBuOH/Moles SecBuOH + moles EtCell
MW SecBuOH = 74g/mol ρ = 0.808g/ml
MW EtCell = 90g/mol ρ = 0.931g/ml

mol fraction SecBuOH = 0.445 =
(X/74g/mol)/ ((X/74g/mol) + (4.1.09g - X)/90g/mol))

X = grams SecBuOH in the product mixture = 0.43g
1.09 - X = grams EtCell in the product mixture = 0.66g

$[\alpha]_{25}$ = α observed/ (pathlength) x (gcmpd./ml)
= -3.00/ (1dm) x (0.43g SecBuOH/1.20ml solution)
= **-8.31**

B. Sample Calculation of Apparent Ratio $B_{ac}2/B_{al}2$ for the Saponification of Optically Active Secondary Butyl Pivaloate-Run 1

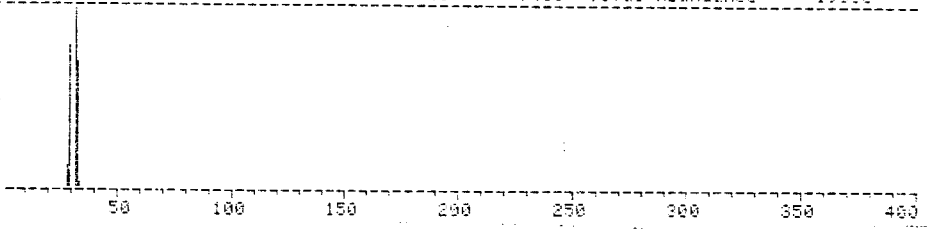
$[\alpha]_{25}$ measured for SecBuOH in Run 1 = -12.51
$[\alpha]_{25}$ SecBuOH literature value = +/- 13.51

let amount of $B_{al}2$ = X then amount $B_{ac}2$ = (1-X)
if only $B_{ac}2$ and $B_{al}1$ occurred then:
-8.31 = +12.51X + -12.51(1-X)

X = 0.17 (1-X) = 0.83 ------> 4.88:1 @ **$4B_{ac}2:1B_{al}2$**

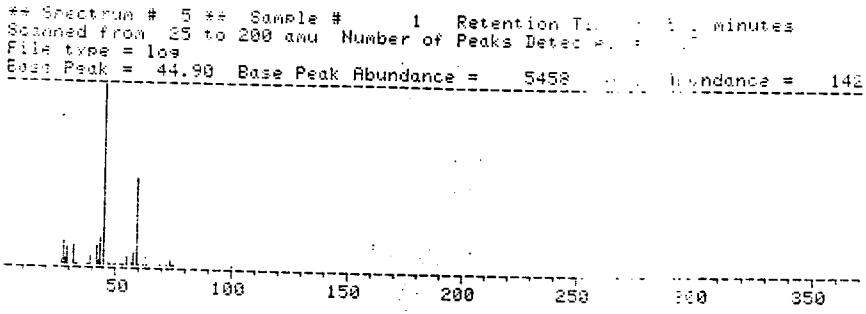
C. Mass Fragementation Patterns for Methanol = CH_3OH

Mass	Fragment
32	CH_3OH^+
31	CH_3O^+



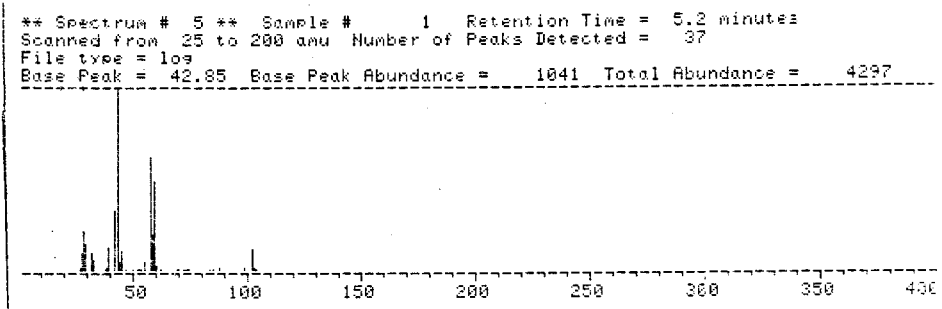
D. Mass Fragementation Patterns for Secondary Butyl Alcohol

Mass	Fragment
74	Molecular Ion
59	M - CH_3
45	M- C_2H_5



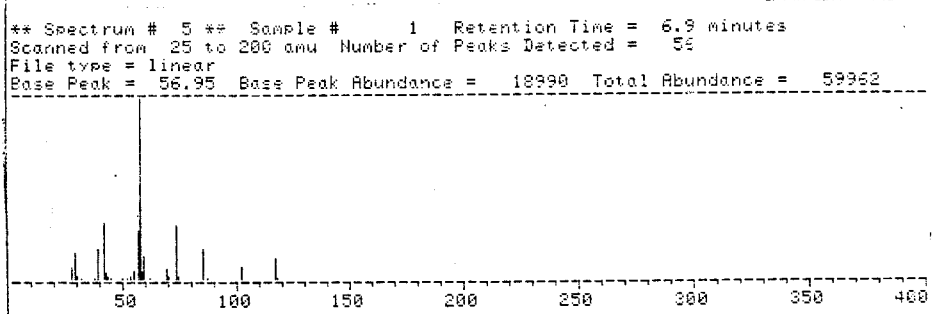
E. Mass Fragementation Patterns for Pivalic Acid

Mass	Fragment
102	Molecular Ion
58	$(CH_3)_3CH^+$
57	$(CH_3)_3C^+$
43	$(CH_3)_2CH^+$



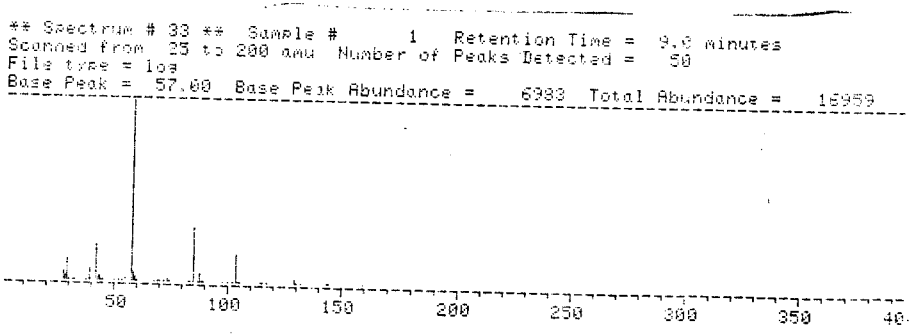
F. Mass Fragmentation Patterns for Methyl Pivaloate

Mass	Fragment
116	Molecular Ion
85	$(CH_3)_3CC{=}O^+$
57	$(CH_3)_3C^+$



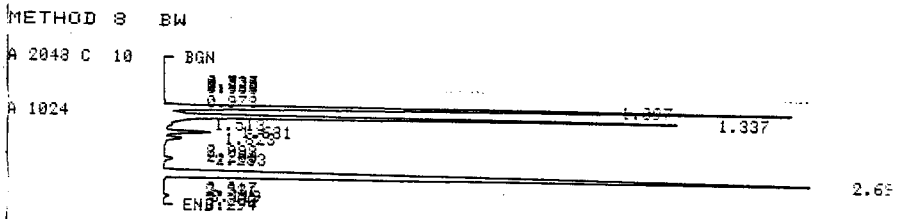
G. Mass Fragmentation Patterns for Secondary Butyl Pivaloate

Mass	Fragment
143	M - CH_3
129	M - C_2H_5
103	$(CH_3)_3CC^+(OH)_2$
85	$(CH_3)_3CC{=}O^+$
57	$C_4H_9^+$ (2° or 3°)
41	$C_3H_5^+$
29	$C_2H_5^+$



H. Gas Chromatogram for a standard quantitative mixture of secondary butyl alcohol, secondary butyl pivaloate, and ethyl cellosolve; calculated response factor(RF) are given - area% now corresponds directly to mole%

Standard Quantitative Mixture = 47.50% secondary butyl alcohol
35.00% ethyl cellosolve
18.50% secondary butyl pivaloate



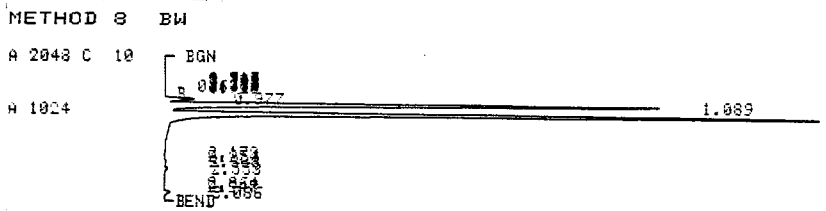
RUN 1 21:27 89/01/17

METHOD S BW CALCULATION: NORM = Mol %

RT	AREA	BC	RRT	RF	AREA %	NAME
1.097	890.7631	T	0.109	0.0005	45.8274	SECBUOH
1.337	385.1083	T	0.133	0.0010	35.1768	ETCELL
2.694	787.5141	T	0.269	0.0002	18.9958	SECBUPIV

3 MATCHED COMPONENTS 99.99% OF TOTAL AREA
0 UNKNOWN >= UNRETD PEAK TIME 0.00% OF TOTAL AREA
3 PEAKS > AREA/HT REJECT

I. Gas Chromatogram for optically active saponification run 2. Only secondary butyl alcohol and ethyl cellosolve peaks are observed, thus saponification has gone to completion.



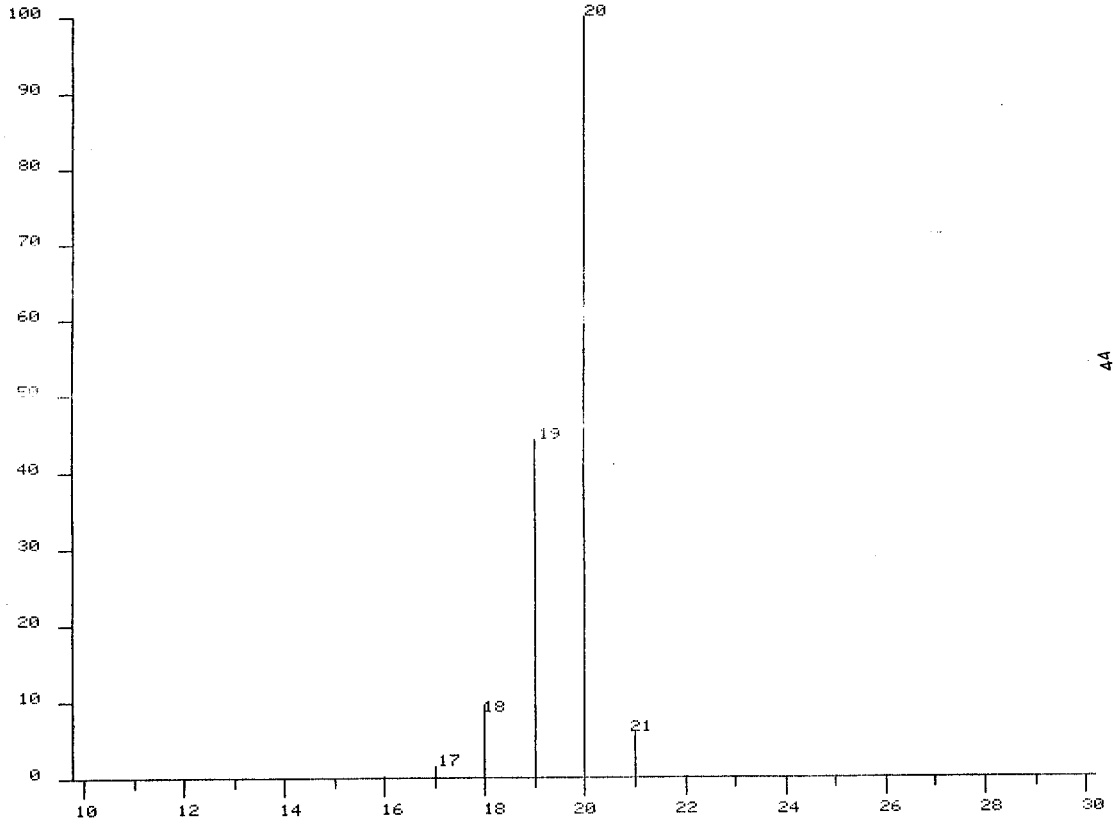
RUN 3 21:40 89/01/17

METHOD 8 BW CALCULATION: NORM

RT	AREA	BC	RRT	RF	AREA %	NAME
1.089	820.8507	T	0.108	0.0005	44.1851	SECBUOH
1.336	584.0163	T	0.133	0.0010	55.8148	ETCELL
			0.266	0.0002		SECBUPIV

2 MATCHED COMPONENTS 100.00% OF TOTAL AREA
0 UNKNOWN >= UNRETD PEAK TIME 0.00% OF TOTAL AREA
2 PEAKS > AREA/HT REJECT

J. Background subtracted mass spectrum of the H_2O^{18} employed in the O^{18} tracer studies.



$H_2C^{13}O$

K. Peak intensities for mass spectrum J.

IONISATION: EI
NO. PEAKS: 27
BASE/NREF INT: 1286592./ 1286592.
TIC: 3506752.
MASS RANGE: 4 - 131
RETN_TIME/MISC: 0: 0/ 0/ 0/ 0

PEAK NO.	MEASURED MASS	NO. POINTS	ABSOLUTE INTENSITY	% INT. BASE	% TOT. ION
1	130.9533	21	1593.	0.1	0.0*
2	118.9513	21	1719.	0.1	0.0*
3	99.9446	8	273.	0.0	0.0
4	68.9518	35	8897.	0.7	0.3
5	50.9700	10	411.	0.0	0.0
6	47.9650	21	2045.	0.2	0.1*
7	45.9639	14	951.	0.1	0.0*
8	43.9598	14	962.	0.1	0.0
9	39.9289	29	4040.	0.3	0.1*
10	35.9622	14	578.	0.0	0.0*
11	33.9523	8	233.	0.0	0.0
12	31.9404	51	82624.	6.4	2.4
13	29.9545	21	2175.	0.2	0.1*
14	28.9684	21	1414.	0.1	0.0*
15	27.9788	59	154132.	12.0	4.4
16	22.0161	12	554.	0.0	0.0
17	21.0084	59	59308.	4.6	1.7*
18	19.9996	71	1286592.	100.0	36.7
19	18.9900	87	491760.	38.2	14.0
20	17.9865	87	111868.	8.7	3.2*
21	16.9824	51	17666.	1.4	0.5*
22	15.9761	43	7654.	0.6	0.2*
23	13.9855	51	9844.	0.8	0.3*
24	7.9940	29	1899.	0.1	0.1*
25	4.0046	14	831.	0.1	0.0*
26	3.9970	207	1254784.	97.5	35.8*
27	3.9921	21	1974.	0.2	0.1*

Basepeak on spectrum is 20

45

Need to compare with the ^{13}C spectrum to calculate abn? 2008
at least 192 abn 2008

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