THE REACTION OF HALOGEN-CONTAINING LEWIS ACIDS WITH ESTERS

by

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THE REACTION OF HALOGEN-CONTAINING LEWIS ACIDS WITH ESTERS

Introduction

Reaction of Halogen-Containing Lewis Acids with Carbohydrates

Non-catalytic displacement reactions involving halogen-containing Lewis acids are an uncommon occurrence in organic chemistry. While such reactions have been investigated outside of carbohydrate chemistry, mechanistic studies are non-existent. While most displacement reactions are best studied in protonic solvents, displacement reactions involving halogen-containing Lewis acids occur most readily in the absence of solvent or in an aprotic solvolytic medium. This raises the question of whether these reactions can be studied in a classical manner.

The first investigations of displacements involving halogen-containing Lewis acids were conducted in the area of carbohydrate chemistry. Displacement reactions of acetylated carbohydrates with halogen-containing Lewis acids, exemplified by equation 1, have been extensively reviewed (98,8,37) and will be discussed only briefly in this section.

$$ROAc + MX_n \longrightarrow RX + M(OAc)X_{n-1} \qquad (1)$$

The first reports of the use of anhydrous aluminum chloride as a reagent in carbohydrate chemistry were those of Arlt (3), and of Skraup and Kremann (86), who in 1901, showed that the mixed anomeric D-glucopyranose pentaacetate

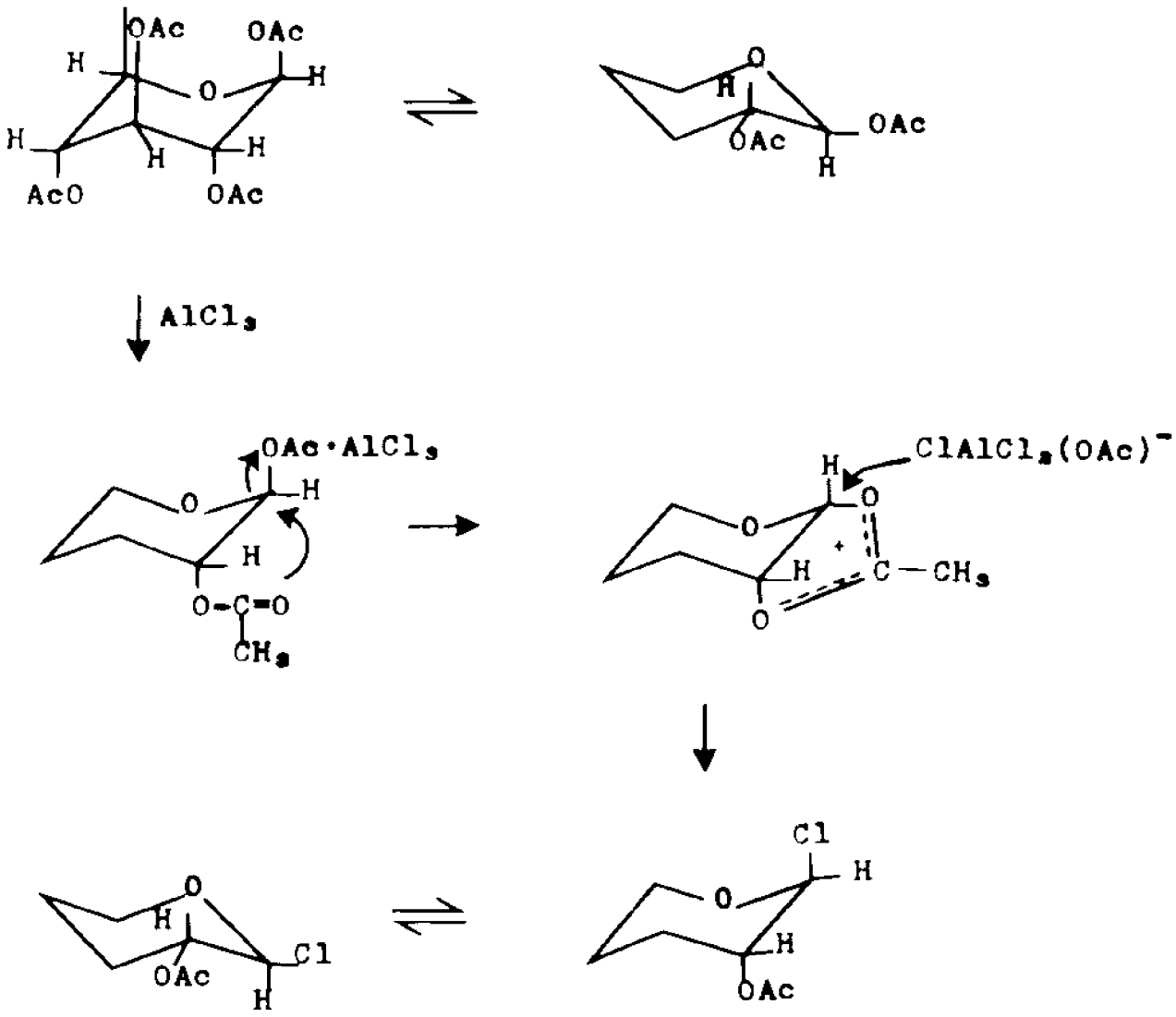
as well as D-galactopyranose pentaacetate yielded the corresponding tetra-O-acetylglycosyl chlorides when their chloroform solutions were heated with a mixture of aluminum chloride and phosphorous pentachloride. Other workers have reported similar displacements at C-1 of acetylated carbohydrates with these reagents. Thus, Hudson and Johnson (41) prepared a tetra-O-acetylgalactofuranosyl chloride from β-D-galactofuranose pentaacetate and Brauns utilized the mixed reagents for the production of comparable derivatives of fructose (9) and mannose (10). Similar preparations have been reported by others (38,22).

That aluminum chloride alone is capable of chlorinating the C-1 position has also been demonstrated. Kunz and Hudson (54) reported that when lactose octaacetate was refluxed with twice its weight of aluminum chloride in dry chloroform, heptaacetyllactosyl chloride was formed. Tetra-O-acetyl-glucopyranosyl chloride was prepared by refluxing anhydrous aluminum chloride with β-D-glucopyranose pentaacetate in dry chloroform (7). The reaction of β-D-glucopyranose penta-acetate with anhydrous aluminum chloride in cold chloroform gave a good yield of the corresponding glycosyl chloride (118,24), while α-D-glucopyranose pentaacetate did not react under the same conditions (98), thus demonstrating the high configurational specificity of the reaction.

This specificity was again emphasized when the treat-ment of a number of anomeric pairs of sugar acetates with

aluminum chloride was studied (50). The fully acetylated β-D- forms of glucopyranose, galactopyranose, galactofuranose, xylopyranose, and the α-D- form of mannopyranose all reacted readily to give the acetylglycosyl chloride of the same configuration as the acetate used, whereas the anomeric acetate was in every case recovered unchanged. Thus, only those sugars with a 1,2-trans configuration reacted in every case to give a product with retention of configuration. The mechanism proposed for this displacement of acetoxy by chlorine was the following: the electrophilic aluminum atom becomes coordinated to one of the oxygens of the 1-acetoxy group and the resulting change in polarity, assisted by electron displacement from the 2-acetoxy group (neighboring group participation), causes transfer of the acetoxy group from position one to the aluminum, resulting in the formation of an acetoxonium ion intermediate (I). Chlorine is then transferred from the ion $AlCl_3(OAc)^-$ to position one, opening the intermediate and forming the product with retention of configuration (50) (Scheme I,p.5).

Scheme I

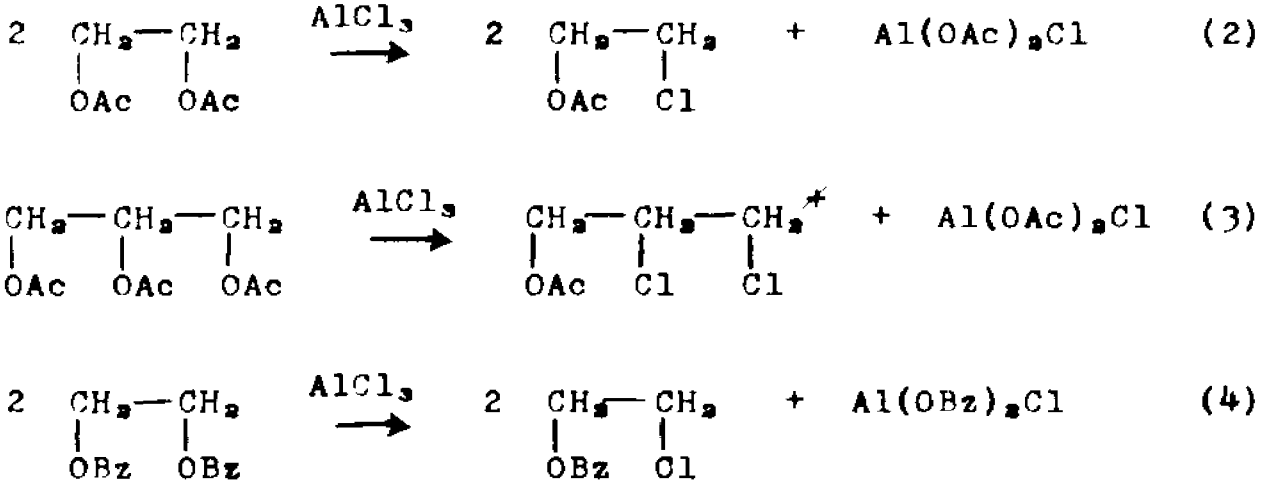

OAc
OAc
H
O
H
H
H
H
AcO
OAc
OAc
H
O
OAc
H
AlCl3
OAc·AlCl3
O
H
H
O-C=O
CH3
ClAlCl3(OAc)-
H
O
O
H
C
CH3
O
Cl
H
O
H
OAc
Cl
H
O
H
OAc

It has also been shown that aluminum chloride causes inversion of configuration at C-2 and C-3 of an acetylated sugar after refluxing in chloroform (54,40,77). This inversion can similarly be explained by the removal of an acetoxy group from $\underline{e,f_{ax}}$, C-2 causing the formation of an acetoxonium ion intermediate between C-2 and C-3. Internal return of the acetate ion to the C-3 position results in inversion of configuration at C-3. With the exception of this isomerization, the reaction of acetylated sugars with Lewis acids under the mild conditions of refluxing in chloroform or carbon tetrachloride illustrates the non-reactivity of the substituent at positions other than C-1. This non-reactivity must be attributed to the ability of the adjacent ring oxygen to stabilize the positive charge that develops at the C-1 position.

Other halogen-containing Lewis acids have been found to cause displacements at C-1 of acetylated aldoses. Titanium tetrachloride is a good reagent for the preparation of acetylated glycosyl chlorides from the corresponding O-acetyl sugars (71). For example, it reacts rapidly with β-D-glucopyranose and only slowly with the α-D-anomer (57), thus demonstrating a similar configurational specificity to that observed in aluminum chloride reactions. Titanium tetrabromide has been used to prepare glycosyl bromides from the corresponding O-acetyl compounds (117).

Reaction of Halogen-Containing Lewis Acids with Polyol Esters

The first reports of the reaction of a halogen-containing Lewis acid with a polyol ester outside of carbohydrate chemistry were those of Dobryanskii and Sivertsev in 1947 who reported the results of the reaction of anhydrous aluminum chloride with various polyol acetates and benzoates (19,85). They heated esters with aluminum chloride for one hour at 150-160°. Their findings were that one carboxylate group always remained resistant to displacement while the rest were replaced by chlorine. Though no quantitative data were provided, the stoichiometry of the reaction was derived from the fact that the recovered aluminum salt was aluminum chlorodiacetate or aluminum chlorodibenzoate. Their results are summarized in equations 2-4.



*Subsequently found to be a mixture of isomers in which the symmetrical isomer predominates (107).

Efforts to displace all of the acetoxy groups of pentaerythritol tetraacetate were also unsuccessful. At best only three of the four groups were displaced. In addition, reaction of aluminum chloride with the chloroester product, e.g., 2-chloroethyl acetate, resulted only in the recovery of starting material. The authors concluded that the resistance of the final ester group to the action of aluminum chloride was a result of an accumulation of negatively charged chlorine atoms in the molecule.

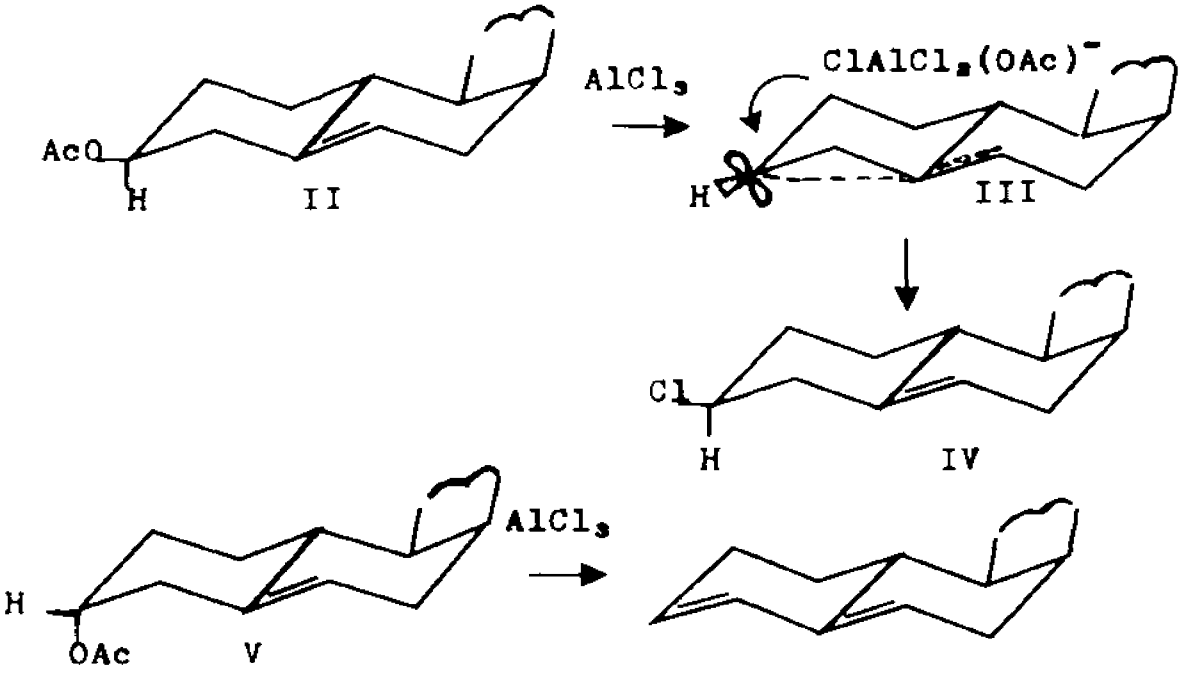
Wilen and Vanderhoek (106,87) proposed a neighboring group participation mechanism similar to that for the reaction of aluminum chloride at C-1 of acetylated carbohydrates (p.5) to explain the results observed by Dobryanskii and Sivertsev. They did not, however, offer any experimental evidence to support their mechanism.

Evidence that the displacement of a carboxylate group by halogen can be assisted by functional groups other than carboxylates is found in the results of the reaction of aluminum chloride with various steroids (11). The reaction between β-cholesteryl acetate (II) (similar results were obtained with alcohols) and aluminum chloride yielded β-cholesteryl chloride (IV). However, with α-epicholesteryl acetate (V) and aluminum chloride an elimination instead of a substitution product was formed. In addition, there was no reaction between cholestan-3-yl acetate (saturated B-ring) and aluminum chloride.

indicating that a center of unsaturation in the vicinity of the acetoxy group is necessary for the displacement to occur (106).

The mechanism proposed to account for the facts is summarised in Scheme II.

Scheme II



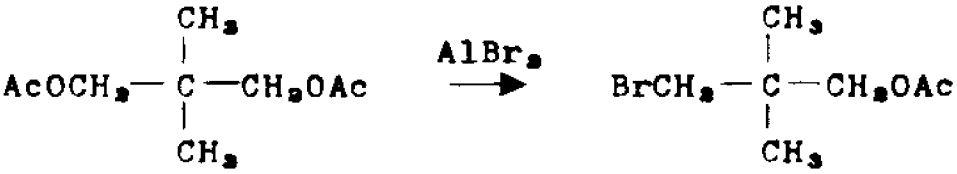
The acetoxy groups of the β-isomer (II) departs with the back-side assistance of the pi electrons of the double bond to form a homoallylic intermediate III. The incoming nucleophile can now attack the C-3 position displacing the homallylic bond leading to β-cholesteryl chloride (IV) with complete overall retention of configuration. The acetoxy group of the α-isomer V is

in an axial conformation and therefore unable to receive backside assistance from the pi-electrons in the B ring.

In an effort to extend the results of Dobryanskii and Sivertsev (p.7) Jedlinskii and Paprotny undertook a study of the reaction of anhydrous aluminum bromide with polyol acetates (47). The reactants were heated at 150-160° for one hour. The results are given in equations 5-8.

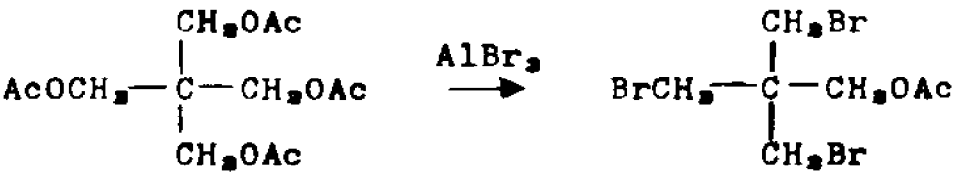
(5)

(6)



(75.5%)

(7)



(8)

These equations indicate that aluminum bromide is more reactive towards esters than aluminum chloride as shown by the fact that it can cause the displacement of all of the carboxylate groups in some polyol esters. While one acetoxy group does remain resistant to attack with the neopentyl-type acetates as illustrated in equations 7 and 8 (p.10), both of the acetoxy groups are displaced in 1,2-ethanediol diacetate and in 1,6-hexanediol diacetate respectively. The displacements in the latter instance apparently proceed without any possibility of neighboring group participation or anchimeric assistance, which would require the unlikely formation of a nine-membered acetoxonium ion.

Protonic (hydrohalic) acids have been successfully used to halogenate polyol esters. However, unlike the aluminum chloride reactions (equations 2-4,p.7) they have been used in many instances to effect displacement of all the carboxylate groups. Generally only in neopentyl-type esters does one of the ester functions remain resistant to displacement. In 1905, Perkin and Simonsen (73) used a solution of hydrobromic acid in acetic acid to brominate polyol acetates. The authors apparently had no difficulty in displacing all of the acetoxy groups of 1,2-ethanediol diacetate, 1,2,3-propanetriol triacetate, and 1,2,3,4-butanetetraol tetraacetate with bromine. In the case of the straight chain mannitol hexaacetate they did report finding it impossible to replace more than five of the acetoxy groups with bromine. The reaction of pentaerythritol tetraacetate with acetic acid

and dry HBr after twenty hours of heating yielded only the di-and tribromo derivatives, thus demonstrating that the bromination proceeded in a stepwise manner until the tribromide stage (82). Similarly it was reported that the chlorination of pentaerythritol with dry HCl was facilitated by the formation of its tetraacetate derivative (99,116). It has also been shown that this reaction can be catalyzed by various Lewis acids (17,21,39,53,100). For example, kinetic studies indicate that the rate of chlorination of pentaerythritol tetraacetate with dry HCl increases 1,000 times in the presence of zinc chloride or ferric chloride and 100 times in the presence of stannous chloride, cobalt (II) chloride, bismuth (II) chloride and aluminum chloride (100). This catalytic effect was attributed to the ability of these Lewis acids to coordinate with the carbonyl oxygen of the acetoxy group thus facilitating its departure. The coordinated Lewis acid must then surrender a chloride ion to complete the process.

A detailed study of the reaction was made with an anhydrous zinc chloride catalyst (100). The results showed that the concentration of zinc chloride remains constant during the reactions and there was a negligible amount of zinc acetate present at any one time. This along with the observation that the chlorination still proceeds fairly rapidly in the absence of HCl gas led the authors to conclude that the chief role of the HCl was to convert the zinc acetate to zinc chloride, the actual chlorinating agent.

The rates of the stepwise chlorination of various acetates with anhydrous zinc chloride and dry HCl as reported by Watanabe, Sugihara and Tanaka are summarized in Table 1 on p.14 (101). The investigators concluded that a neopentyl-type of monoacetate is sterically hindered from coordinating its acetoxy group with zinc chloride and thus is chlorinated with difficulty; however when there are at least two acetoxy groups present to sandwich the zinc chloride, coordination is facilitated thus increasing the rate of chlorination. No mention was made of the possible involvement of a neighboring group effect. The observation that the relative rate of reaction of 1,3-propanediol diacetate to that of 3-chloropropyl acetate is only 15 as compared to a relative rate of 217 for 2,2-dimethyl-1,3-propanediol diacetate to 2,2-dimethyl-3-chloropropyl acetate was not explained, though the evidence would seem to indicate that the monoacetates undergo an S_N2 displacement, recalling that S_N2 substitution rates decline markedly with α-alkyl substitution (88).

Table I: Rates of Chlorination of Alkyl Acetates (0.334 mole) by $ZnCl_2$ (0.081 mole) and HCl (500 cc./min.) at 160°

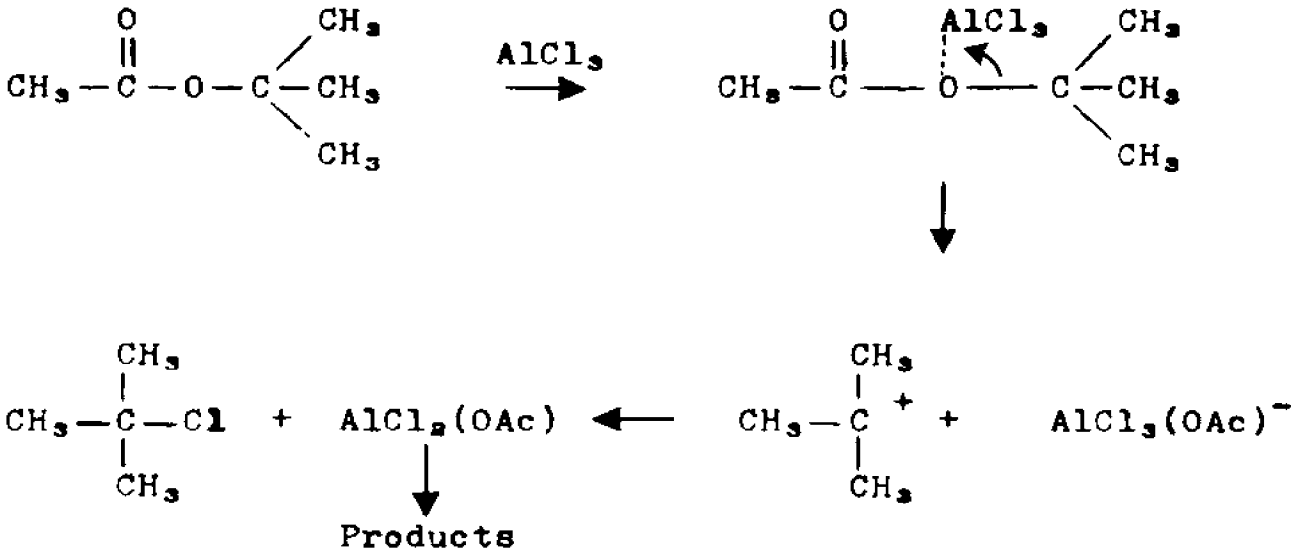
Reactant	Product	Rate (min^{-1})	Relative Rate
$C_9H_{19}CH_2OAc$*	$C_9H_{19}CH_2Cl$	0.96×10^{-2}	
$C_{11}H_{23}CH_2OAc$*	$C_{11}H_{23}CH_2Cl$	1.0×10^{-2}	
$CH_2(OAc)-CH_2-CH_2(OAc)$	$CH_2(OAc)-CH_2-CH_2Cl$	3.0×10^{-2}	15
$CH_2(OAc)-CH_2-CH_2Cl$	$CH_2Cl-CH_2-CH_2Cl$	2.0×10^{-3}	
$(CH_3)_2C(CH_2OAc)_2$	$(CH_3)_2C(CH_2OAc)(CH_2Cl)$	1.6×10^{-2}	217
$(CH_3)_2C(CH_2OAc)(CH_2Cl)$	$(CH_3)_2C(CH_2Cl)_2$	7.4×10^{-5}	

*Evidently normal isomer

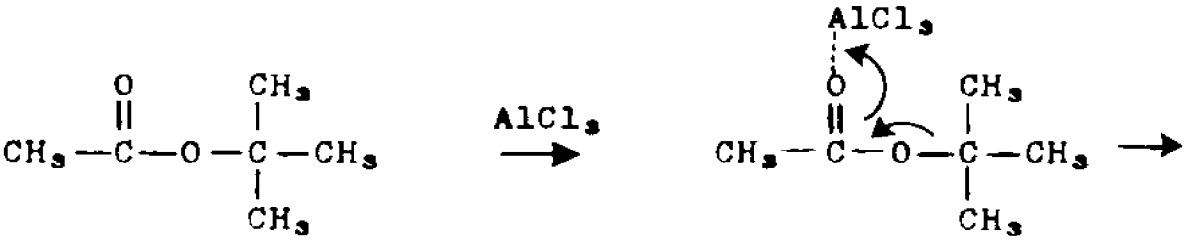
Reaction of Lewis Acids with Monoesters

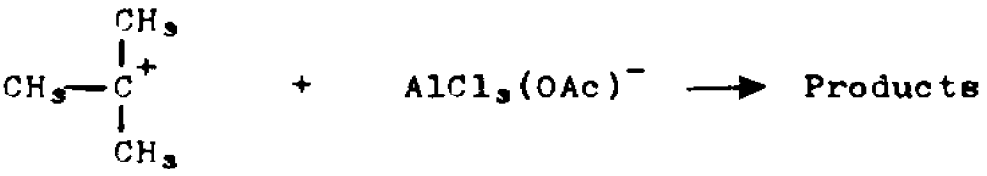
There have been many reports of the reaction of various halogen-containing Lewis acids with saturated monoesters. Few conclusions can be drawn, for in many cases the reaction conditions are not comparable. The heating of aluminum chloride with various chlorinated primary acetates and benzoates gave no observable products (19,85). However, the reaction of n-butyl acetate with aluminum chloride at 300-330° yielded 1-chlorobutane along with unsaturated hydrocarbons (26,27). Norris and Arthur heated aluminum chloride with methyl acetate for 2.5 hours at an unreported temperature and obtained a yield of 70% chloromethane (67). Ethyl acetate yielded 85% 1-chloroethane after 6.3 hours of heating. Reaction of n-butyl acetate with aluminum chloride at 170° gave 1-chlorobutane (5%) and butenes (67). Ethyl benzoate gave 1-chloroethane in 95% yield after 5 hours of heating at 150-155° with aluminum chloride (68). Illari reported 1-chloroethane as a product when ethyl acetate was heated with aluminum chloride at 100° (45). Mehrotra and Misra found that refluxing aluminum chloride in a large excess of tert-butyl acetate at 110° produces aluminum triacetate and tert-butyl chloride (61). The mechanism that was proposed is outlined in Scheme III (p.16).

Scheme III



Or





Aluminum triacetate and tert-butyl bromide were obtained from the reaction of aluminum bromide and tert-butyl acetate under similar conditions (63), while titanium tetrachloride gave $TiCl_3(OAC)_3$ and tert-butyl chloride when refluxed with excess tert-butyl acetate (62). A similar mechanism to that shown in Scheme III (p.16) was proposed in both cases.

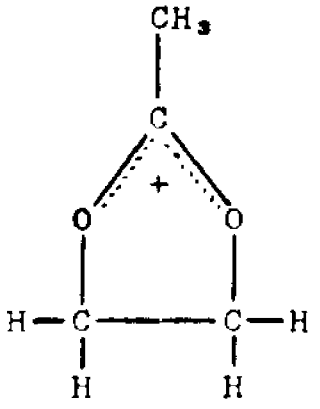
When ethyl formate, propionate and n-butyrate are refluxed with anhydrous zinc chloride for two hours, the esters remain unchanged (94), while 2-propyl benzoate gives 22% 2-chloropropane along with 15% propene (95).

Gerrard and Frazer have used boron trichloride to halogenate various monoacetates. They reported that heating ethyl acetate with boron trichloride at 100° gives a yield of 45.4% ethyl chloride (28). When boron trichloride was heated with optically active secondary acetates the recovered chlorinated product was predominantly inverted in configuration with some loss of optical activity; olefinic side products were also present. It thus appeared that this displacement could have been at least partially S_N1 in character (32).

Neighboring Group Participation - The Acetoxonium Ion

Neighboring acetoxy group participation has served as an important tool to explain reaction mechanisms in different areas of organic chemistry as has been pointed out by several reviewers (56,60,14,44,1).

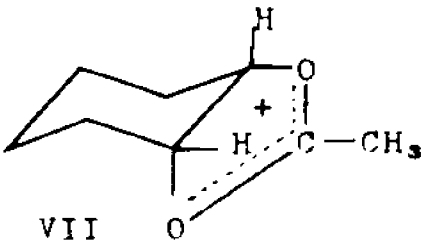
An acetoxonium ion like the 2-methyl-1,3-dioxolenium cation (VI) was first formulated in 1942 by Winstein and Buckles (108).



VI

Winstein and Buckles treated trans-2-bromocyclohexyl acetate with silver acetate in dry acetic acid and after hydrolysis isolated 1,2-cyclohexanediol which was 98% trans. Optically active trans-2-bromocyclohexyl acetate gave the same trans-diacetate, but it was racemic. When optically active 2-bromooctane was subjected to these same conditions, 2-octyl acetate was obtained. The stereochemical results were 86% inversion and 14% retention. This is the expected result from a S_N1 process. A S_N2 process should give

inversion exclusively. Because optically active trans-2-bromocyclohexyl acetate yielded nearly pure trans-diacetate with complete loss of optical activity, this reaction could not have been an S_N1 or S_N2 process. The results were explained by the formation of the symmetrical acetoxonium ion intermediate VII.



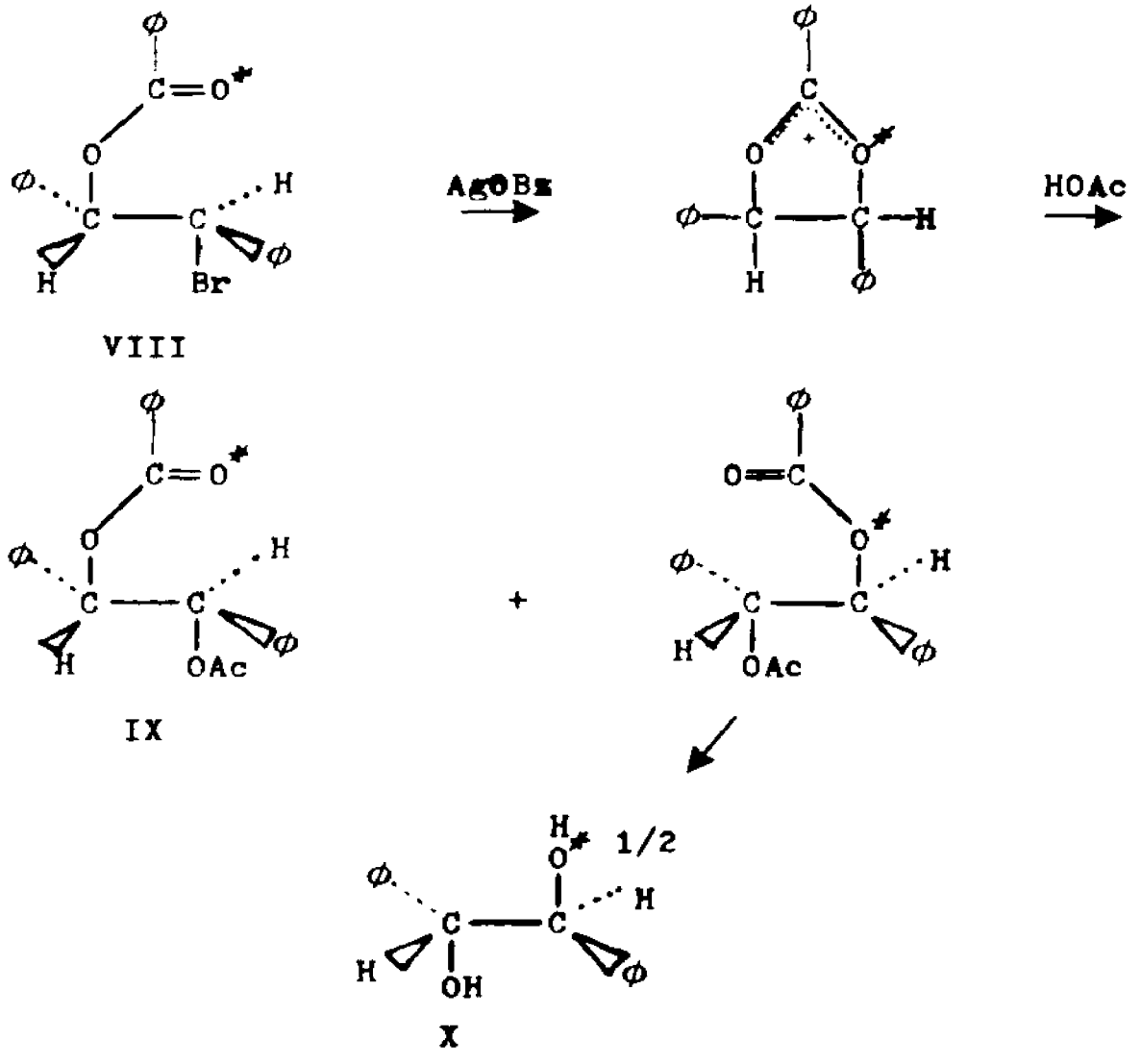
VII

A large difference in reactivity between trans-and cis-2-chlorocyclohexyl acetates in reaction with silver acetate was noticed. Winstein and Buckles concluded that the participating trans acetoxy group must supply a driving force which makes the reaction proceed more easily. The rate of acetolysis of trans-2-acetoxycyclohexyl brosylate was found to be 650 times faster than that of the cis-isomer at 100° (111). The energy of activation necessary for acetoxy participation has been calculated to be 4.6 kcal/mole (113).

Acetolysis of trans-2-acetoxycyclohexyl tosylate in the presence of potassium acetate was also found by Winstein, Hess and Buckles (114) to give trans-1,2-cyclohexanediol diacetate in high purity, and they again postulated the intervention of the acetoxonium ion (VII).

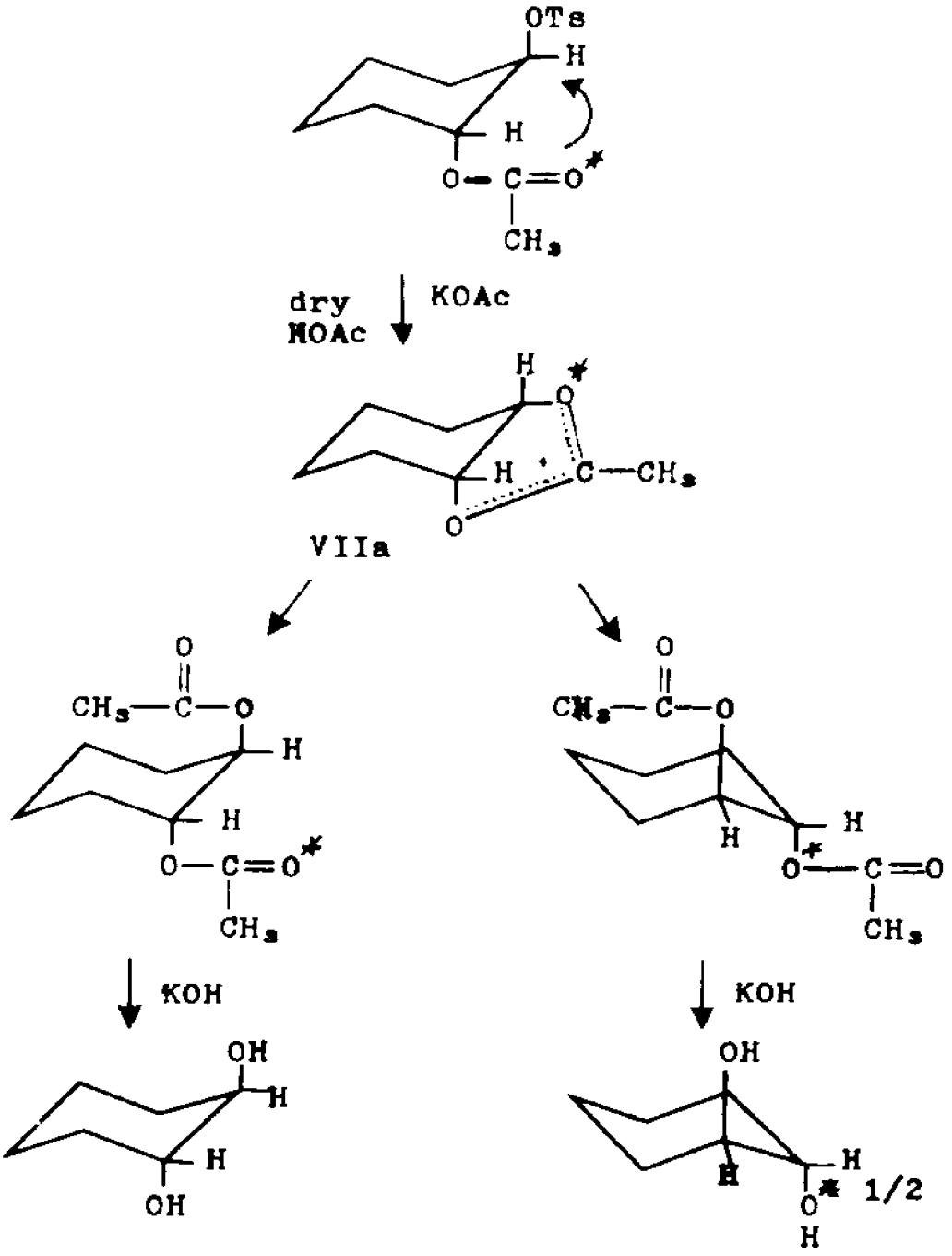
In 1957 Wiberg and Saegebrath (105) confirmed the course of the Winstein mechanism by experiments utilizing compounds labelled with oxygen-18. They treated <u>erythro</u>-2-bromo-1,2-diphenylethyl benzoate (VIII) labelled in the carbonyl oxygen, with silver benzoate in dry acetic acid. The product was a diester (IX) which after saponification gave <u>meso</u>-hydrobenzoin (X) containing half the amount of O-18 in the original benzoxybromide (VIII)(Scheme IV).

<u>Scheme IV</u>

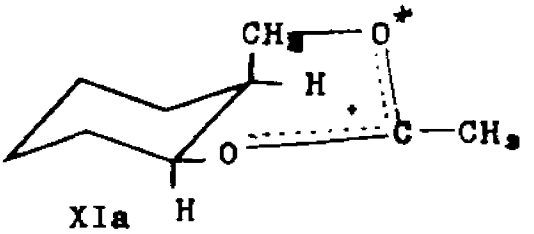


Gash and Yuen (25) studied the solvolysis of carbonyl-O^{18} labelled trans-2-acetoxy cyclohexyl tosylate with potassium acetate in dry acetic acid as a means of confirming the role of the acetoxonium ion intermediate VIIa in the acetolysis of trans-2-acetoxycyclohexyl tosylate (Scheme V).

Scheme V



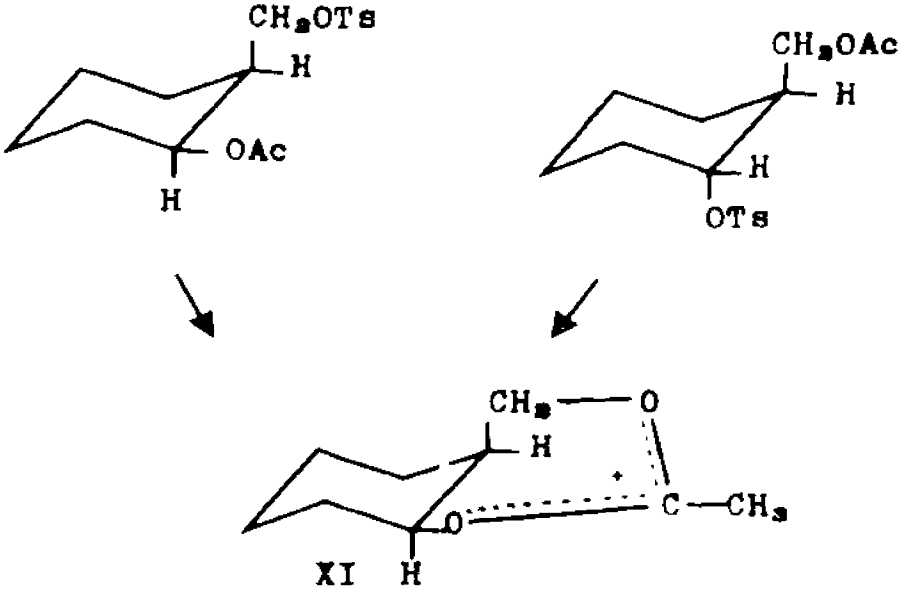
O-18 Labeling has also been used to confirm the existence of six-membered acetoxonium ions, e.g., XIa (20).



XIa

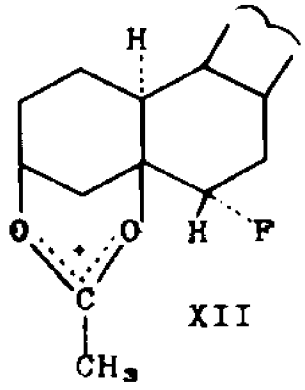
In comparison to the large number of examples of AcO-5 participation, only a few cases of AcO-6 participation are known. A study of the kinetics and stereochemistry of the acetolysis of cis-2-tosyloxymethylcyclohexyl acetate and trans-2-acetoxymethylcyclohexyl tosylate confirms that these solvolyses pass through the six-membered acetoxonium ion intermediate XI (Scheme VI)(20,84,52,51).

Scheme VI



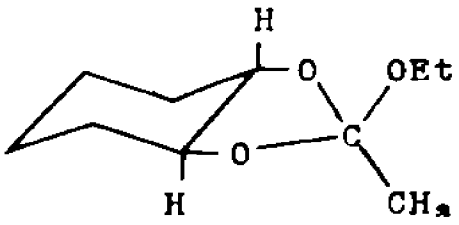
XI

Reactions involving the steroidal intermediate XII have been extensively studied (6,16) as another example of a six-membered acetoxonium ion.



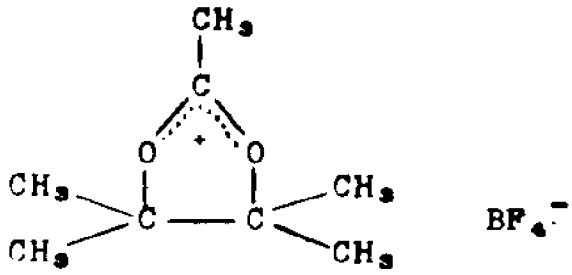
XII

Important evidence supporting the existence of the acetoxonium ion VII (p.19) in the solvolysis of <u>trans</u>-2-acetoxycyclohexyl tosylate in dry ethanol and in the presence of potassium acetate, was the trapping of the intermediate as the ethyl orthoacetate XIII (110).



XIII

Further confirmation of the existence of acetoxonium ions has been obtained by their successful isolation. Winstein and co-workers have prepared the tetrafluoroborate salt of the 2-methyl-cis-tetramethylene-1,3-dioxolenium ion (XIV) and confirmed its chemical properties (2).



XIV

Similarly the tetrafluoroborate salt of the six-membered acetoxonium ion XI has been isolated (84). Olah has prepared the 2-methyl-1,3-dioxolenium cation XIV from 2-halo-3-acetoxy-2,3-dimethylbutanes in antimony pentafluoride-sulfur dioxide, and in antimony pentafluoride-fluorosulfonic acid-sulfur dioxide solutions, and has examined its nmr spectrum at temperatures of -60° and below (69). The tetrafluoroborate salts of various derivatives of the acetoxonium ion VI (p.18) were prepared and their nmr spectra studied in SO_2 at -20° and in FSO_3H at room temperature (36). The nmr spectra observed were consistent with the structures previously proposed for the respective acetoxonium ions.

The Problem

Mechanistic studies on the reaction of polyol esters with anhydrous aluminum chloride have been undertaken in order to confirm the postulate (106,97) that the reactions in question, in which all but one of the ester functional groups are displaced by the action of aluminum chloride, involved neighboring group participation. The reaction of *cis*- and of *trans*-1,2-cyclohexanediol diacetate with anhydrous aluminum chloride was investigated as a means of determining the validity of the proposed mechanism. In addition, oxygen-18 labeling studies of the reactions of aluminum chloride, zinc chloride, and zinc chloride-HCl with various polyol acetates have been undertaken in order to determine the extent of neighboring group participation.

The evidence for unassisted displacement of carboxylates by halogenated Lewis acids is both fragmentary and in some cases contradictory. This type of displacement was investigated by studying the products, stereochemistry, and relative rates of reactions of aluminum chloride, aluminum bromide, zinc chloride-HCl with various mono and polyol esters.

EXPERIMENTAL

General

All materials whose preparations are not described were purchased commercially and distilled or recrystallized when necessary after spectroscopic and/or gas chromatographic analysis. Anhydrous aluminum chloride (reagent grade) was purchased from J. T. Baker Chemical Co. Anhydrous aluminum bromide, purchased from Fisher Scientific Co., was purified by sublimation under dry nitrogen. Anhydrous zinc chloride was purchased from City Chemical Corp. Oxygen-18 enriched un-normalized* water was purchased from Bio-Rad Laboratories in 5% concentration and Miles Laboratories, Inc. in 3.84% concentration.

Melting points were determined on a Thomas-Hoover apparatus and are corrected; boiling points are uncorrected. A Nester-Faust NFT-50 Annular Teflon spinning band column was used for fractional distillation where indicated.

Spectra were determined on the following instruments: infrared, Perkin-Elmer 137 Infracord (absorption maxima are expressed in reciprocal centimeters, cm^{-1}, and their intensities abbreviated as follows: strong (s), medium (m), weak (w), very weak (vw)); nuclear magnetic resonance, Varian A-60 (chemical shifts are expressed in δ (ppm) downfield from internal tetramethylsilane (δ =0)). Rotations

*Deuterium content exceeds natural abundance

were measured on a Perkin-Elmer 141 Photoelectric Polarimeter.

Gas-liquid chromatography (g.c.) was performed on a F & M Model 720, dual column instrument utilizing thermal conductivity detectors with helium as carrier gas. The analyses were carried out with the following columns: Column A, 10 ft. x 0.25 in. O.D. copper column packed with 20% carbowax 20 M on 60/80 mesh chromosorb W; Column B, 16 ft. x 0.25 in. O.D. copper column packed with 20% diethylene glycol adipate on 60/80 mesh chromosorb P; Column C, 10 ft. x 0.25 in. O.D. stainless steel column packed with 10% LAC-728 on 60/80 mesh chromosorb W. The areas of g.c. peaks were measured with a planimeter or with a Honeywell Disc Chart Integrator, Model 201-B.

O-18 Analyses were performed either by Isotopes Inc. of Westwood, New Jersey, or at the laboratory of Dr. D. Rittenberg of Columbia University, The College of Physicians and Surgeons, New York City.

Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Preparation of 1,3-Propanediol Diacetate

A solution consisting of 20.0 g. (0.26 mole) of 1,3-propanediol and 52.0 g. (0.66 mole) of dry pyridine in 100 ml. of chloroform was placed in a 250-ml. three-necked flask equipped with a condenser fitted with a drying tube, and a pressure-equalizing addition funnel. Acetyl chloride, (52.0 g., 0.66 mole) was added to this solution over a period of 0.5 hr. The solution was stirred magnetically at 40° for 14 hrs. and poured into 50 ml. of 0.5N hydrochloric acid. The chloroform layer was washed with 50 ml. of 10% aqueous sodium bicarbonate and 50 ml. of water, dried over magnesium sulfate, filtered, and the solvent removed (rotary evaporator). The residue was distilled to yield 27.0 g. (64%) of clear, colorless product: b.p. 91-94° (10 mm.) (lit.(48) b.p. 91-92° (10 mm.)); ir (liquid film): 2990 (m, alkyl-H), 1730 (s, carbonyl), 1360 (s, methyl), 1230, 1040 cm^{-1} (s, C-O-C); nmr ($CDCl_3$): 1.80-2.30 (multiplet, 2 H, methylene), 2.10 (singlet, 6 H, acetate methyl), 4.20 ppm (triplet, J = 6.5 Hz, 4 H, oxymethylene).

Preparation of 3-Chloropropyl Acetate

The acetylation was carried out as in the case of 1,3-propanediol diacetate (p.28). The reaction of 20.0 g. (0.21 mole) of 3-chloropropanol and 21.0 g. (0.27 mole) of dry pyridine with 21.0 g. (0.27 mole) of acetyl chloride in 100 ml. of chloroform at 70° for 4 hrs. yielded 17.0 g. (59%) of clear, colorless product: b.p. 61-63° (13 mm.) (lit.(58) b.p. 62-63° (10 mm.)); ir (liquid film): 2990 (m, alkyl-H), 1750 (s, carbonyl), 1390, 1370 (m, methyl) 1240, 1040 cm^{-1} (s, C-O-C); nmr ($CDCl_3$): 2.10 (quintuplet, J = 6.2 Hz, 2 H, methylene), 2.08 (singlet, 3 H, acetate methyl), 3.65 (triplet, J = 6.2 Hz, 2 H, chloromethylene), 4.23 ppm (triplet, J = 6.2 Hz, 2 H, oxymethylene).

Preparation of 1,4-Butanediol Diacetate

This was carried out in the manner described on p.28. The reaction of 34.0 g. (0.38 mole) of 1,4-butanediol and 83.0 g. (1.03 mole) of dry pyridine with 81.0 g. (1.05 mole) of acetyl chloride in 350 ml. of chloroform at 25° for 4 hrs. yielded 36.0 g. (54%) of clear, colorless product: b.p. 58-61° (0.4 mm.) (lit.(96) b.p. 106° (15 mm.)); ir (liquid film): 2990 (m, alkyl-H), 1750 (s, carbonyl), 1390, 1370 (m, methyl) 1240, 1040 cm^{-1} (s, C-O-C); nmr ($CDCl_3$): 1.68 multiplet, 4 H, methylene), 2.00 (singlet, 6 H, acetate methyl), 4.08 ppm (multiplet, 4 H, oxymethylene).

Preparation of 1,5-Pentanediol Diacetate

The acetylation was carried out in a manner similar to that described on p. 28. Stirring 10.0 g. (0.10 mole) of 1,5-pentanediol and 22.0 g. (0.28 mole) of dry pyridine with 20.0 g. (0.27 mole) of acetyl chloride in 200 ml. of chloroform for 12 hrs. at 25° yielded 10.0 g. (53%) of clear, colorless product: b.p. 69-71° (0.4 mm.) (lit.(65) b.p. 122° (12 mm.)); ir (liquid film): 2990 (m, alkyl-H), 1750 (s, carbonyl), 1390, 1370 (m, methyl), 1240, 1040 cm^{-1} (s, C-O-C); nmr ($CDCl_3$): 1.50-1.80 multiplet, 6 H, methylene), 2.05 (singlet, 6 H, acetate methyl), 4.10 ppm (triplet, J = 6.0 Hz, 4 H, oxymethylene).

Preparation of 1,6-Hexanediol Diacetate

Carried out as described on p.28. Stirring 30.0 g. (0.25 mole) of 1,6-hexanediol and 60.0 g. (0.76 mole) of dry pyridine with 55.0 g. (0.70 mole) of acetyl chloride in 200 ml. of chloroform for 2 hrs. at 25° yielded 40.0 g. (79%) of clear, colorless product: b.p. 73-75° (0.4 mm.) (lit.(76) b.p. 119-121° (4.5 mm.)); ir (liquid film): 2990, 2970, (s, alkyl-H), 1750 (s, carbonyl), 1390, 1360 (m, methyl), 1240, 1040 cm^{-1} (s, C-O-C); nmr ($CDCl_3$): 1.20-1.80 (multiplet, 8 H, methylene), 2.00 (singlet, 6 H, acetate methyl), 4.08 ppm (triplet, J = 6.0 Hz, 4 H, oxymethylene).

Preparation of 2,2-Dimethyl-1,3-propanediol Diacetate

2,2-Dimethyl-1,3-propanediol (50.0 g., 0.48 mole) was acetylated as described on p.28 by adding 110.0 g. (1.4 mole) of dry pyridine and stirring with 103.0 g. (1.4 mole) of acetyl chloride in 250 ml. of chloroform for 18 hrs. at 25°. The yield was 54.0 g. (60%) of clear, colorless product: b.p. 51-52° (0.8 mm.) (lit.(70) b.p. 100° (20 mm.)); ir (liquid film): 2990, 2970 (m, alkyl-H), 1750 (s, carbonyl), 1380 (s, methyl), 1240, 1040 cm^{-1} (s, C-O-C); nmr $CDCl_3$): 0.95 (singlet, 6 H, methyl), 2.05 singlet, 6 H, acetate methyl), 3.90 ppm (singlet, 4 H, oxymethylene).

Preparation of 2,2-Dimethylpropyl Acetate

Prepared from 2,2-dimethylpropanol as described on p.28. A solution consisting of 34.0 g. (0.39 mole) of 2,2-dimethylpropanol, 40.0 g. (0.51 mole) of dry pyridine, and 40.0 g. (0.51 mole) of acetyl chloride in 200 ml. of chloroform was refluxed for 18 hrs. to yield 23.0 g. (46%) of clear, colorless product: b.p. 125-127° (lit.(81) b.p. 127° (740 mm.)); ir (liquid film): 2980, (s, alkyl-H), 1740 (s, carbonyl), 1370 (s, methyl), 1240 (s, C-O-C), 1040, 1020 cm^{-1} (m, C-O-C); nmr ($CDCl_3$): 0.95 (singlet, 9 H, methyl), 2.08 (singlet, 3 H, acetate methyl), 3.80 ppm (singlet, 2 H, oxymethylene).

Preparation of (+)-(S)-2-Octyl Acetate

Prepared as described on p.28. Stirring of 10.0 g. (0.08 mole) of (+)-(S)-2-octanol, $[\alpha]^{25}D$ +9.35° (1 dm., neat)(lit.(75) $[\alpha]^{20}D$ +9.76° (neat)), purchased from the Aldrich Chemical Co., and 10.0 g. (0.13 mole) of dry pyridine with 10.0 g. (0.13 mole) of acetyl chloride in 100 ml. of n-hexane at room temperature for 24 hrs. yielded 8.3 g. (68%) of clear, colorless product: b.p. 79-80° (11 mm.), $[\alpha]^{24}D$ +6.20° (1 dm., neat), $[\alpha]^{27}D$ +3.03° (c 1.03, chloroform) (lit.(108,43,33) b.p. 81.3-82° (12.5 mm.), $[\alpha]^{20}D$ +7.48° (neat), $[\alpha]^{25}D$ +6.5° (c 5.3, 95% ethanol)). The infrared spectrum (liquid film) was identical to that reported for the racemic acetate (80).

Preparation of 2-Chloroethyl Acetate

To a 200-ml. three-necked flask equipped with a condenser fitted with a drying tube and a pressure-equalizing addition funnel, were added 55.0 g. (0.68 mole) of 2-chloroethanol and 250 ml. of n-hexane. Acetyl chloride (87.0 g., 1.10 mole) was added dropwise over a period of 1 hr. while the reaction mixture was stirred magnetically. The mixture was then stirred for an additional 2.5 hrs. at 25°. The solvent was removed (rotary evaporator) and the residue was distilled to yield 71.5 g. (81%) of clear, colorless product: b.p. 145-147° (lit.(46) b.p. 141-142° (738 mm.)); ir (liquid film): 2990 (w, alkyl-H), 1750 (s, carbonyl), 1380, 1360 (m, methyl), 1240, 1040 (s, C-O-C), below 650 cm^{-1} (s, C-Cl); nmr ($CDCl_3$): 2.13 (singlet, 3 H, acetate methyl), 3.70 (triplet, J = 5.5 Hz, 2 H, chloromethylene), 4.35 ppm (triplet, J = 5.5 Hz, 2 H, oxymethylene).

Preparation of *trans*-1,2-Cyclohexanediol Diacetate

The acetylation was carried out in a manner similar to that described on p.33. The reaction of 52.0 g. (0.45 mole) of *trans*-1,2-cyclohexanediol with 143 g. (1.8 mole) acetyl chloride in 200 ml. of *n*-hexane at room temperature for 22 hrs. yielded 62.5 g. (70%) of clear, colorless product: b.p. 78-82° (1.5 mm.) (lit.(108) b.p. 120° (12 mm.)); ir (liquid film): 2980, 2970 (m, alkyl-H), 1740 (s, carbonyl), 1370 (m, methyl), 1240, 1040 cm^{-1} (s, C-O-C): nmr ($CDCl_3$): 1.20-2.20 (multiplet, 8 H, ring methylenes), 2.00 (singlet, 6 H, acetate methyl), 4.68-5.00 ppm (multiplet, 2 H, 1- and 2-H). G.c. analysis (column B at 190°, 60 cc./min.) showed no *cis* isomer to be present.

Preparation of cis-1,2-Cyclohexanediol Diacetate

(1) Preparation of cis-1,2-Cyclohexanediol

Catechol (200 g., 1.8 mole), dissolved in 300 ml. of absolute ethanol, was hydrogenated at 125° and at an initial hydrogen pressure of 2000 p.s.i. in the presence of 10 g. of 5% ruthenium on carbon in a 1-liter glass lined and stirred autoclave (Autoclave Engineers, Inc.). The hydrogen pressure was permitted to drop to 1200 p.s.i. before it was returned to the initial pressure. When hydrogen absorption was complete the reaction mixture was filtered from the catalyst and the solvent removed (rotary evaporator) to give a residue which was recrystallized three times from carbon tetrachloride. Yield: 51.0 g. (24%) of a white solid: m.p. 97.5-98.8° (lit.(109) m.p. 98°)); nmr ($CDCl_3$): 1.20-1.90 (multiplet, 8 H, ring methylenes), 3.13 (singlet, 2 H, hydroxyl), 3.60-3.90 ppm (multiplet, 2 H, 1- and 2-H). The infrared spectrum (KBr) was identical with that reported (79).

(2) Preparation of *cis*-1,2-Cyclohexanediol Diacetate

This was prepared in a manner similar to that described on p.33. Stirring 23.0 g. (0.20 mole) of *cis*-1,2-cyclohexanediol (p.35) with 60.0 g. (0.78 mole) of acetyl chloride in 200 ml. of *n*-hexane at room temperature for 17 hrs. yielded 27.2 g. (68%) of clear, colorless product: b.p. 77-80° (1.5 mm.) (lit.(108) b.p. 117.8-118.0° (12 mm.)); ir (liquid film): 2990, 2970, (m, alkyl-H), 1740 (carbonyl), 1360 (m, methyl), 1240 (s, C-O-C), 1050, 1020 cm^{-1} (m, C-O-C); nmr ($CDCl_3$): 1.40-2.20 (multiplet, 8 H, ring methylenes), 2.05 (singlet, 6 H, acetate methyl), 4.88-5.18 ppm (multiplet, 2 H, 1- and 2-H). G.c. analysis (Column B at 190°, 60 cc./min.) showed less than 1% of the *trans* isomer to be present.

Preparation of trans-2-Chlorocyclohexyl Acetate

(1) Preparation of trans-2-Chlorocyclohexanol

To a 1-l. two-necked flask equipped with a condenser and a pressure-equalizing addition funnel were added 150 g. (1.5 mole) of cyclohexene oxide and 250 ml. of diethyl ether. The solution was stirred magnetically at 0° while 150 g. (1.6 mole) of concentrated hydrochloric acid was slowly added; stirring was continued at room temperature for 14 hrs. The aqueous layer was salted out of solution with sodium chloride and extracted with six 25-ml. portions of ether. The combined ethereal extract was dried over magnesium sulfate, filtered, and the solvent removed (rotary evaporator). Vacuum distillation of the residue yielded 128 g. (62%) of clear, colorless product: b.p. 75° (10 mm.) (lit. (87) 88-89° (20 mm.)). The infrared spectrum (liquid film) was identical to that reported (87).

(2) Preparation of trans-2-Chlorocyclohexyl Acetate

The acetylation was carried out in a manner similar to that described on p.33. The reaction of 38.0 g. (0.30 mole) of trans-2-chlorocyclohexanol (p.37) and 35.0 g. (0.45 mole) of acetyl chloride in 150 ml. of n-hexane at room temperature for 20 hrs. yielded 19.0 g. (36%) of clear, colorless product: b.p. 95.5-96.5° (10 mm.) (lit. (112) b.p. 98-98.5° (12 mm.)); ir (liquid film): 2990, 2970 (m, alkyl-H), 1750 (s, carbonyl), 1450 (m, methylene), 1380, 1360 (m, methyl), 1240 (s, C-O-C), 1050, 1040 cm^{-1} (m, C-O-C); nmr ($CDCl_3$): 1.20-2.30 (multiplet, 8 H, ring methylenes), 2.13 (singlet, 3 H, acetate methyl), 3.65-4.05 (multiplet, 1 H, 2-H), 4.60-5.05 ppm (multiplet, 1 H, 1-H).

Preparation of cis-2-Chlorocyclohexyl Acetate

(1) Preparation of cis-2-Chlorocyclohexanol

Prepared by modification of the procedure of Stevens and Grummitt (87). Sodium borohydride (6.0 g., 0.16 mole) and 100 ml. of absolute ethanol were placed in a 200-ml. three-necked flask equipped with a condenser, a pressure-equalizing addition funnel, and a mechanical stirrer. A solution of 41.0 g. (0.31 mole) of 2-chlorocyclohexanone in 100 ml. of anhydrous ethanol was added over a period of 0.5 hr. The reaction mixture was heated at 60° for 2 hrs., 1.5 l. of 0.2N sodium hydroxide added, and the mixture stirred at 0° for 0.5 hr. The solution was then extracted with five 200-ml. portions of diethyl ether. The combined ether washings were dried over magnesium sulfate, filtered, and the solvent was removed (rotary evaporator). Vacuum distillation of the residue yielded 23.0 g. (56%) of clear, colorless product: b.p. 72-75° (10 mm.) (lit.(112) 92.5-93° (27 mm.)). The infrared spectrum (liquid film) was identical to that reported (87).

(2) Preparation of cis-2-Chlorocyclohexyl Acetate

Prepared in the manner described on page 33. The reaction of 23.0 g. (0.17 mole) of cis-2-chlorocyclohexanol (p.39) with 33.0 g. (0.42 mole) of acetyl chloride in 100 ml. of n-hexane for 1.5 hr. at 80° yielded 16.0 g. (40%) of a clear, colorless liquid; b.p. 94-96° (10 mm.) (lit. (112) b.p. 98.3-99° (12 mm.)); ir (liquid film): 2990, 2970, (m, alkyl-H), 1750 (s, carbonyl), 1450 (m, methylene), 1370, 1350 (m, methyl), 1230 (s, C-O-C), 1040 cm^{-1} (m,C-O-C); nmr ($CDCl_3$): 1.30-2.30 (multiplet, 8 H, ring methylenes), 2.13 (singlet, 3 H, acetate methyl), 4.20-4.50 (multiplet, 1 H, 2-H), 4.83-5.10 ppm (multiplet, 1 H, 1-H). G.c. analysis (column B at 170°, 60 cc./min.) showed the presence of 10% of the trans isomer.

Preparation of *cis*-1,2-Dichlorocyclohexane

Prepared according to a reported procedure (87). Thionyl chloride (49.0 g., 0.41 mole) was added dropwise over a period of 0.5 hr. to a 200-ml. three-necked flask equipped with a condenser fitted with a drying tube, a pressure-equalizing addition funnel, a mechanical stirrer, and containing a stirred mixture of 17.0 g. (0.12 mole) of *trans*-2-chlorocyclohexanol (p.37) and 3.2 g. (0.04 mole) of dry pyridine. The mixture was refluxed for 3 hrs., after which it was poured into 50 ml. of water. The organic layer was separated, washed with three 25-ml. portions of 10% aqueous sodium bicarbonate and 25 ml. of water, and dried over calcium chloride. Filtration and distillation of the crude product yielded 2.6 g. (14%) of a clear, colorless liquid: b.p. 74–77° (10 mm.) (lit. (87) b.p. 103° (30 mm.)). G.c. analysis (column A at 180°, 45 cc./min.), with commercial *trans*-1,2-dichlorocyclohexane as a reference, indicated a *cis*:*trans* ratio of 6:1. The infrared spectrum (liquid film) compared favorably to that which was reported by Stevens and Grummitt for *cis*-1,2-dichlorocyclohexane (87).

Preparation of 5-Chloropentyl Acetate

This ester was prepared by a modification of the procedure of Millington and Pattison (65). A 100-ml. three-necked flask equipped with a condenser fitted with a drying tube, and a pressure-equalising addition funnel was charged with 5.0 g. (0.037 mole) of anhydrous zinc chloride and 30.0 g. (0.35 mole) of dry tetrahydrofuran at 0°. Acetyl chloride (22.0 g., 0.28 mole) was added with stirring over a period of 1 hr. followed by heating at 90° for 15 min. The reaction mixture was poured into 100 ml. of benzene, washed with 100 ml. of 10% aqueous sodium bicarbonate and 100 ml. of a saturated sodium chloride solution. Drying of the benzene solution over magnesium sulfate, filtration, and removal of the benzene (rotary evaporator) gave a residue which yielded 21.0 g. (36%) of a clear, colorless liquid after distillation: b.p. 95° (10 mm.) (lit.(65) b.p. 96-98° (11 mm.)); ir (liquid film): 2990, 2970 (m, alkyl-H), 1740 (s, carbonyl), 1360 (m, methyl), 1240 (s, C-O-C), 1040 cm^{-1} (m, C-O-C); nmr ($CDCl_3$): 1.20-1.90 (multiplet, 6 H, methylene), 2.05 (singlet, 3 H, acetate methyl), 3.58 (triplet, J = 6.0 Hz, 2 H, chloromethylene), 4.08 ppm (triplet, J = 6.5 Hz, 2 H, oxymethylene).

Preparation of 6-Chlorohexyl Acetate

This compound was prepared as described on p.42 from anhydrous zinc chloride (2.5 g., 0.018 mole), 1-oxacycloheptane (18.0 g., 0.18 mole) and 11.0 g. (0.14 mole) of acetyl chloride. Yield: 13.0 g. (52%); b.p. 70-71° (0.8 mm.) (lit.(64) b.p. 88-90° (3 mm.)); ir (liquid film): 2990, 2970 (m, alkyl-H), 1750 (s, carbonyl), 1370 (m, methyl), 1240 (s, C-O-C), 1040 cm^{-1} (m, C-O-C); nmr ($CDCl_3$): 1.20-1.90 (multiplet, 8 H, methylene), 2.00 (singlet, 3 H, acetate methyl), 3.53 (triplet, J = 6.3 Hz, 2 H, chloromethylene), 4.08 ppm (triplet, J = 6.0 Hz, 2 H, oxymethylene).

Preparation of 6-Bromohexyl Acetate

This compound was prepared in the manner described on p.42. The reaction of anhydrous zinc bromide (4.5 g., 0.02 mole), and 1-oxacycloheptane (20.0 g., 0.20 mole) with 20.0 g. (0.16 mole) of acetyl bromide yielded 16.0 g. (43%) of a clear, colorless liquid; b.p. 83-84° (1.5 mm); ir (see p.77) (liquid film): 2990, 2970 (m, alkyl-H), 1750 (s, carbonyl), 1460, 1440, 1390 (w, methylene, methyl), 1360 (m, methyl), 1240 (s, C-O-C), 1040 (m, C-O-C), 730 cm^{-1} (w); nmr ($CDCl_3$): 1.30-1.90 (multiplet, 8 H, methylene), 2.03 (singlet, 3 H, acetate methyl), 3.45 (triplet, J = 6.5 Hz, 2 H, bromomethylene), 4.10 ppm (triplet, J = 6.5 Hz, 2 H, oxymethylene).

Anal. Calcd. for $C_8H_{15}O_2Br$: C, 43.09; H, 6.73; Br, 35.84; O, 14.35. **Found:** C, 43.29; H, 6.76; Br, 35.90; O (direct), 14.40.

Preparation of 2,2-Dimethyl-1,3-dibromopropane

This compound was prepared by a reported procedure (103). A 250-ml. three-necked flask equipped with a condenser, a pressure-equalizing addition funnel, and a mechanical stirrer, was charged with 25.0 g. (0.25 mole) of 2,2-dimethyl-1,3-propanediol at 0°. Phosphorus tribromide (70.0 g., 0.26 mole) was added dropwise with stirring over a period of 1 hr. Upon completion of the addition, the reaction mixture was allowed to warm to room temperature and then heated at 150-160° for 30 hrs. A red precipitate was formed during this time. The reaction mixture was poured into 250 ml. of water and extracted with three 100 ml. portions of diethyl ether. The combined ether extract was washed with two 50-ml. portions of 10% aqueous sodium bicarbonate and 50 ml. of water, dried over magnesium sulfate, and filtered. Removal of the ether (rotary evaporator) and distillation of the residue led to a yield of 4.0 g. (7%) of a clear, colorless liquid: b.p. 64-65° (10 mm.) (lit.(103) 84° (28 mm.)); ir (liquid film): 2990 (s, alkyl-H), 1470, 1420 (m, methyl, methylene), 1380, 1365 (m, methyl), 1260 (s), 675 cm^{-1} (m, bromine); nmr ($CDCl_3$): 1.18 (singlet, 6 H, methyl), 3.43 ppm (singlet, 4 H, methylene).

Preparation of 2,2-Dimethyl-3-bromopropyl Acetate

Prepared by modification of a reported procedure (102). A 500-ml. three-necked flask equipped with a condenser was charged with 38.0 g. (0.37 mole) of 2,2-dimethyl-1,3-propanediol, 190 ml. of glacial acetic acid, and 5 ml. of 47-48% hydrobromic acid. The solution was heated to reflux for 1.5 hrs. An additional 43 ml. of 47-48% hydrobromic acid was added and the reaction mixture was refluxed for three more hours. The mixture was extracted with three 100-ml. portions of diethyl ether and the combined ether extract was neutralized with 10% aqueous sodium carbonate, washed with 100-ml. of water, dried over magnesium sulfate, and filtered. Removal of the solvent (rotary evaporator) and distillation of the residue yielded 24.0 g. of a clear, colorless liquid: b.p. 84-85° (10 mm.) (lit.(4) 83° (8 mm.)). The infrared spectrum (liquid film) indicated the presence of an alcohol. Acetylation of this product with 22.0 g. (0.28 mole) of acetyl chloride in 100 ml. of chloroform at room temperature for 1.5 hrs. followed by removal of the chloroform (rotary evaporator) yielded 24.0 g. of a clear, colorless liquid free of alcohol. G.c. analysis (Column C at 130°, 60 cc./min.) showed one major peak (80% by peak area) and two minor peaks. The major peak was collected by preparative g.c. (Column C at 120°, 60 cc./min.): ir (liquid film): 2990 (m, alkyl-H), 1740 (s, carbonyl), 1460, 1390 (m, methyl, methylene), 1370 (s, methyl), 1240, 1040 cm^{-1}

(s, C-O-C); nmr ($CDCl_3$): 1.08 (singlet, 6 H, methyl), 2.08 (singlet, 3 H, acetate methyl), 3.35 (singlet, 2 H, bromomethylene), 3.95 ppm (singlet, 2 H, oxymethylene).

Preparation of 3-Chlorooctane

To a 100-ml. three-necked flask equipped with a condenser fitted with a drying tube, a pressure-equalizing addition funnel, and a mechanical stirrer were added 5.0 g. (0.038 mole) of 3-octanol, 4.5 g. (0.06 mole) of dry pyridine, and 20 ml. of chloroform. Thionyl chloride (6.9 g., 0.06 mole) was added to the stirred mixture in 20 minutes and the whole was refluxed for 6 hrs. The reaction mixture was poured into 100 ml. of 0.5N hydrochloric acid. The chloroform layer was separated, washed with 10 ml. of 10% aqueous sodium bicarbonate and 10 ml. of water, dried over magnesium sulfate and filtered. Distillation yielded 1.7 g. (30%) of a clear, colorless liquid: b.p. 54-55° (12 mm.) (lit.(5) b.p. 67.5-68° (20 mm.)); nmr ($CDCl_3$): 0.70-1.15 (triplet, J = 7.0 Hz, 6 H, methyl), 1.15-2.00 (multiplet, 10 H, methylene), 3.85 ppm (quintuplet, J = 6.0 Hz, 1 H, C-3 methine).

Preparation of 4-Chlorooctane

This compound was prepared from 4-octanol as described above. The reaction of 5.0 g. (0.04 mole) of 3-octanol, 5.0 g. (0.06 mole) of dry pyridine, and 7.0 g. (0.06 mole) of thionyl chloride yielded 2.0 g. (35%) of clear, colorless product: b.p. 55° (10 mm.) (lit.(59) 92° (50 mm.)); nmr ($CDCl_3$): 0.70-1.15 (multiplet, 6 H, methyl), 1.20-2.00 (multiplet, 10 H, methylene), 3.88 ppm (quintuplet, J = 5.5 Hz, 1 H, C-4 methine).

Preparation of Acetyl Chloride-O^{18}

Acetyl chloride (52.2 g., 0.66 mole) was placed in a 250-ml. three-necked flask equipped with a condenser and a pressure-equalizing addition funnel. The magnetically stirred acetyl chloride was kept at 0° while 10.0 g. (0.55 mole) of water-O^{18} (5% or 3.84% O^{18} enrichment) was added over a period of 45 min. The reaction mixture was heated at 55° for 2 hrs., and allowed to cool gradually to room temperature. With the condenser capped by a drying tube, thionyl chloride (65.0 g., 0.55 mole) was slowly added to the stirred mixture over a period of 30 min., and the reaction mixture then heated at 40-45° for 2.5 hrs. One milliliter of glacial acetic acid was added in order to insure the complete reaction of the thionyl chloride, and the heating continued for 1 hr. Distillation yielded 38.5 g. (89%) of acetyl chloride-O^{18}, b.p. 35-54°, which was used without further purification.

Preparation of 1,2-Ethanediol Diacetate-O^{18}

The acetylation of 1,2-ethanediol was carried out as described on p.28. The reaction of 7.8 g. (0.13 mole) of 1,2-ethanediol, 24.0 g. (0.31 mole) of dry pyridine, and 23.0 g. (0.30 mole) of acetyl chloride-O^{18} (p.49) in 100 ml. of chloroform yielded 11.5 g. (63%) of a clear, colorless liquid: b.p. 78-80° (10 mm.) (lit.(92) b.p. 188.8-190.3). G.c. analysis (column A at 160°, 45 cc./min.) showed the product to have a purity in excess of 99%. The infrared spectrum (liquid film) was identical to that of the corresponding unlabelled compound. The product was analyzed for O^{18} content (p.67). The O^{18} concentration is tabulated on pp.92 and 99.

Preparation of 1,3-Propanediol Diacetate-O^{18}

1,3-Propanediol (9.3 g., 0.12 mole) was acetylated with 24.0 g. (0.31 mole) of acetyl chloride-O^{18} (p.49) as described on p.28. The yield was 27.0 g. (64%) of clear, colorless product: b.p. 94-95° (11 mm.) (lit.(48) b.p. 91-92° (10 mm.)). G.c. analysis (column A at 170°, 45 cc./min.) showed the product to have a purity in excess of 99%. The infrared spectrum (liquid film) was identical to that of the corresponding unlabelled compound (p.28). The product was analyzed for O^{18} content (p.67). The results are tabulated on pp. 93,100, and 101.

Preparation of cis-1,2-Cyclohexanediol Diacetate-O^{18}

The acetylation of 9.2 g. (0.08 mole) of cis-1,2-cyclohexanediol (p.34) with 16.0 g. (0.20 mole) of acetyl chloride-O^{18} (p.49) was carried out essentially as described on p.28. Fractional distillation of the product with a spinning band distillation column yielded 8.9 g. (56%) of a clear, colorless liquid: b.p. 78° (1.3 mm.) (lit.(108) b.p. 117.8-118.0° (12 mm.)). G.c. analysis (column A at 170°, 45 cc./min. and column B at 190°, 60 cc./min.) showed the absence of the trans isomer; product purity was estimated to be greater than 98%. The infrared spectrum (liquid film) was identical to that of the corresponding unlabelled compound (p.36). The O^{18} content was analyzed (p.67). The results are tabulated on p.97.

Preparation of trans-1,2-Cyclohexanediol Diacetate-O^{18}

The acetylation of trans-1,2-cyclohexanediol (14.6 g., 0.13 mole) with 24.7 g. (0.32 mole) acetyl chloride-O^{18} (p.49) was carried out essentially as described on p.28. The yield was 18.9 g. (75%) of a clear, colorless liquid: b.p. 79-80° (1.3 mm.) (lit.(108) b.p. 120° (12 mm.)). G.c. analysis (see above) revealed the absence of the cis isomer; product purity was estimated to be greater than 99%. The infrared spectrum (liquid film) was identical to that of the corresponding unlabelled diacetate (p.34). The O^{18} concentration is tabulated on p.97.

Reaction of Esters with Aluminum Halides

(1) Reaction of Aluminum Chloride with Primary Acetate Esters

A typical reaction was carried out as follows. A 15-ml. three-necked flask equipped with a condenser fitted with a drying tube, a pressure-equalising addition funnel, and a mechanical stirrer, was charged with 11.0 mmoles. of anhydrous aluminum chloride and cooled to 0°. The stirrer was started and the acetate ester (22.5 mmoles.) was quickly added. The reaction mixture was immediately heated, whereupon it turned dark-brown. Heating and stirring was continued at 150-160° for 1 hr. The reaction was quenched by adding 5 ml. of methylene chloride or chloroform and 10 ml. of 0.5N hydrochloric acid.

Product Analysis

The organic layer was analyzed by g.c. The results are tabulated in Tables III and XVIII on pp. 79 and 113, respectively. All products were identified by comparison of retention times with those of known standards, and infrared analysis of fractions recovered from the O^{18} labeling experiments (pp. 61-63). Quantitative analyses were performed by the internal standard method with 1-pentyl acetate serving as the reference. The g.c. conditions and retention times of compounds analyzed are summarized below for the primary acetate ester reactions studied:

(1) 1,2-Ethanediol Diacetate

Column A at 140°, 60 cc./min.; 2-chloroethyl acetate (4.2 min.) and 1,2-ethanediol diacetate (10.6 min.).

(2) 2-Chloroethyl Acetate

Column A at 140°, 60 cc./min.; 1,2-dichloroethane (1.2 min.) and 2-chloroethyl acetate (4.2 min.).

(3) 1,3-Propanediol Diacetate

Column A at 170°, 45 cc./min.; 3-chloropropyl acetate (3.3 min.) and 1,3-propanediol diacetate (8.6 min.).

(4) 1,4-Butanediol Diacetate

Column A at 170°, 60 cc./min.; 4-chlorobutyl acetate (6.9 min.), and 1,4-butanediol diacetate (14.2 min.).

(5) 1,5-Propanediol Diacetate

Column A at 180°, 60 cc./min.; 5-chloropentyl acetate (6.9 min.) and 1,5-propanediol diacetate (13.4 min.).

(6) 1,6-Hexanediol Diacetate

Column A at 190°, 60 cc./min.; 1,6-dichlorohexane (4.0 min.), 6-chlorohexyl acetate (7.3 min.), and 1,6-hexanediol diacetate (13.5 min.).

(7) n-Butyl Acetate

Column A at 90°, 45 cc./min.; 2-chlorobutane (1.2 min.),

1-chlorobutane (1.7 min.), and n-butyl acetate (6.4 min.). The ratio of 1-chlorobutane to 2-chlorobutane was determined with column A at 60°, 45 cc./min. and with the assumption that both response constants were equal.

(2) Reaction of Aluminum Chloride with Cyclohexyl Acetate Esters

The reactions were carried out essentially as described on p.52. Anhydrous aluminum chloride (2.9 mmoles.) and a cyclohexyl acetate (5.8 mmoles.) were heated and stirred together at 150-160° for 1 hr. The flask was allowed to cool to room temperature and the reaction mixture was dissolved in 6.79 g. (52 mmoles.) of 1-pentyl acetate.

Product Analysis

The homogeneous 1-pentyl acetate solution was analyzed by g.c. (column B at 190°, 60 cc./min.). The data have been tabulated in Tables IV,V,VI on pp. 85-87, respectively. All products were identified by comparing retention times with those of known standards, and infrared analysis of fractions recovered from O^{18} labeling experiments (pp. 65-66). The retention times are summarized in Table II (p.56).

Table II: Retention Times of Cyclohexyl Acetate Esters and Their Reaction Products - Column B at 190°, 60 cc./min.

Compound	Time (min.)
(1) trans-1,2-cyclohexanediol diacetate	29.2
(2) cis-1,2-cyclohexanediol diacetate	27.2
(3) trans-2-chlorocyclohexyl acetate	18.7
(4) cis-2-chlorocyclohexyl acetate	19.2
(5) trans-1,2-dichlorocyclohexane	9.5
(6) cis-1,2-dichlorocyclohexane	15.5

At a column temperature of 190°, complete resolution of cis- and trans-1,2-cyclohexanediol diacetate was possible. Cis- and trans-2-chlorocyclohexyl acetate could not however, be completely separated under those conditions. Column B at 170°, 60 cc./min. gave a minimum detectable isomer ratio of 15:1.

Quantitative analysis was performed by the internal standard method with 1-pentyl acetate serving as the reference.

(3) Reaction of Aluminum Bromide with Primary Acetate Esters

A typical reaction was carried out as follows: A 25-ml. three-necked flask equipped as described on p.52 and flushed with dry nitrogen was charged with 3.5 mmoles. of anhydrous aluminum bromide and kept at 0°. The nitrogen flow was discontinued and 7.0 mmoles. of a primary acetate ester quickly added with stirring. The mixture was immediately heated whereupon it turned dark-brown. Heating and stirring were continued for 1 hr. at a temperature of 150-160°. The reaction was quenched by adding 5 ml. of methylene chloride and 10 ml. of 0.5N hydrochloric acid.*

Product Analysis

The methylene chloride layer was analyzed by g.c. The data are tabulated in Tables XIV,XV,XVI,XVII on pp. 103,106,110 and 111, respectively. The products were identified by comparison of retention times with those of known compounds and by infrared analysis of fractions recovered by preparative g.c. Quantitative analysis was performed by the internal standard method. G.c. conditions, retention times for the compounds analyzed, and internal standards utilized are summarized below for the primary acetate ester reactions studied.

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*The 1,2-ethanediol reaction products were not hydrolyzed as this caused a substantial loss of product.

(1) 1,2-Ethanediol Diacetate

Column C at 95°, 60 cc./min. The internal standard was 1-butyl acetate. The following compounds were analyzed: 1,2-dibromoethane (2.8 min.), 2-bromoethyl acetate (7.7 min.), and 1,2-ethanediol diacetate (18.0 min.).

(2) 1,6-Hexanediol Diacetate

Column C at 165°, 60 cc./min. The internal standard was 4-chlorobutyl acetate. The following compounds were analyzed: 1,6-dibromohexane (3.2 min.), 6-bromohexyl acetate (4.6 min.), and 1,6-hexanediol diacetate (6.6 min.).

(3) 2,2-Dimethyl-1,3-propanediol Diacetate

Column C at 120°, 60 cc./min. The internal standard was 1,6-dibromohexane. The following compounds were analyzed: 2,2-dimethyl-3-bromopropyl acetate (4.7 min.) and 2,2-dimethyl-1,3-propanediol diacetate (7.1 min.).

(4) 2,2-Dimethyl-1-propyl Acetate

Column A at 90°, 60 cc./min. The internal standard was 1-pentyl acetate. The following compound was analyzed: 2,2-dimethyl-1-propyl acetate (4.2 min.).

(5) n-Butyl Acetate

Column A at 90°, 60 cc./min. The internal standard was 1-pentyl acetate. The following compounds were analyzed: 2-bromobutane (1.9 min.), 1-bromobutane (2.5 min.), and n-butyl acetate (4.9 min.). The ratio of 1-bromobutane to 2-bromobutane was determined with column A at 60°, 60 cc./min., and with the assumption that their response constants were equal.

Control Reactions

1) Reaction of Aluminum Bromide with 2,2-Dimethyl-1,3-dibromopropane

The reaction was carried out as described on p.57. Anhydrous aluminum bromide (0.87 g., 3.3 mmoles.) and 1.6 g. (6.5 mmoles.) of 2,2-dimethyl-1,3-dibromopropane were heated at 153 ± 2° for one hour. The reaction was quenched by adding 10 cc. of methylene chloride and 10 ml. of 0.5N hydrochloric acid. Examination of the organic layer by g.c. (Column C at 120°, 60 cc./min.) showed the complete absence of starting material with no detectable identifiable products.

2) Reaction of Aluminum Bromide with Bromo-2,2-dimethylpropane or 2-Bromo-2-methylbutane

The reaction was carried out as described above. The bromide reactant (2.6 mmoles.) was stirred with 10.6 mmoles. of aluminum bromide for 1 hr. at 107 ± 1°. Upon completion of the heating, ten microliters were removed from the reaction flask and analyzed by g.c. (Column A at 60°, 45 cc./min.). Neither starting material nor products were detected by gas chromatography. The reaction mixtures were hydrolyzed by adding 10 cc. of chloroform and 10 cc. of 0.5N hydrochloric acid. The organic layers were concentrated and examined by nmr ($CDCl_3$). Similar spectra were obtained for both residues: 0.7-1.3 (multiplet, methyl), 1.5-2.0 ppm (multiplet, methylene).

Reaction of Aluminum Chloride with 1,2-Ethanediol Diacetate-O^{18}

The reaction was performed as described on p.52. Anhydrous aluminum chloride (1.6 g., 12.2 mmoles.) and 1,2-ethanediol diacetate-O^{18} (p.50) (3.5 g., 24.0 mmoles.) were heated and stirred together at 104 ± 2° for 0.5 hr. G.c. analysis (column A at 140°, 45 cc./min.) indicated that the reaction had proceeded to 80% completion. The reaction was quenched by adding 15 ml. of diethyl ether and 5 ml. of water. The aqueous layer was washed with two 10-ml. portions of ether and the combined ether extract was washed with 10 ml. of 10% aqueous sodium bicarbonate. The ether was dried over magnesium sulfate, filtered and removed by distillation. A clear, colorless liquid, (1.3 g.) was obtained by vacuum distillation: b.p. 49-50° (10 mm.). G.c. analysis indicated that the distillate was 90% 2-chloroethyl acetate and 10% 1,2-ethanediol diacetate. The residue (0.5 g.) a yellow oil, consisted of 85-90% 1,2-ethanediol diacetate and 5-10% 2-chloroethyl acetate (g.c. analysis).

Reduction of 2-Chloroethyl Acetate-O^{18}, 2-Chloroethanol-O^{18}

The distillate (above) was dissolved in 10-ml. of anhydrous diethyl ether and slowly added to a solution of 0.24 g. (11 mmoles.) of lithium borohydride in 10 ml. of anhydrous diethyl ether. The reaction mixture was

stirred at room temperature for 3 hrs. and hydrolyzed by addition of 1 ml. of methanol and 1 ml. of water. Ten ml. of methylene chloride was added and the filtered reaction mixture was distilled in order to remove the solvent. The residue yielded 150 mg. of a clear, colorless liquid by preparative g.c. (column A at 115°, 60 cc./min.). Product purity was estimated to be higher than 99% by g.c. analysis. The infrared spectrum (liquid film) was identical to that of commercial 2-chloroethanol. The g.c. recovered sample was analyzed for O^{18} content as described on p.67. The results are tabulated on p.92.

Hydrolysis of Recovered 1,2-Ethanediol Diacetate-O^{18}
Conversion to 1,2-Ethanediol Dibenzoate-O^{18}

The yellow residue obtained (p.61) was added to a solution consisting of 1.6 g. (29 mmoles.) of potassium hydroxide dissolved in 100 ml. of water. The mixture was stirred at room temperature for 2 hrs. The flask was cooled to 0° and 0.7 g. (5 mmoles.) of benzoyl chloride was quickly added to the stirred reaction mixture. Rapid stirring was maintained for 10 min. while a white solid precipitated. The solid product was filtered and recrystallized three times from n-hexane. Crystallization was induced each time by immersion of the n-hexane solution in a dry-ice acetone bath. The white, crystalline product (39 mg.) had a m.p. of 70-71° (lit.(65) m.p. 70.5-71°). The infrared spectrum (KBr) was identical to that of standard

1,2-ethanediol dibenzoate. The product was analyzed for O^{18} content (p.67). The results are tabulated on p.92.

Reaction of Aluminum Chloride with 1,3-Propanediol Diacetate-O^{18}

The reaction and reduction were carried out as described on pp.61-62. Anhydrous aluminum chloride (1.7 g., 13.0 mmoles.) and 1,3-propanediol diacetate-O^{18} (4.3 g., 26.9 mmoles.)(p.50) were heated and stirred together at 106 ± 2° for 1.25 hrs. G.c. analysis (column A at 175°, 45 cc./min.) showed the reaction to have proceeded to 65% completion. The distillate was prepared for O^{18} analysis as described on pp.61-62. The 1,3-propanediol diacetate and 3-chloropropanol were analyzed for O^{18} content (p.67). The results are tabulated on p.93.

Reaction of Aluminum Chloride with *cis*- and *trans*-1,2-Cyclohexanediol Diacetate-O^{18}

The reactions were essentially carried out as described on pp. 52 and 61. Anhydrous aluminum chloride (2.0 g., 14.8 mmoles.) and 6.2 g. (31 mmoles.) of *trans*-1,2-cyclohexanediol diacetate-O^{18} (p.51) were heated at 110-114° for 1 hr. After hydrolysis and extraction, 1.5 g. of a clear, colorless liquid was obtained by vacuum distillation: b.p. 95-100° (12 mm.). G.c. analysis (column B, at 190°, 60 cc./min.) indicated that the major component of the distillate was *trans*-2-chlorocyclohexyl acetate. The residue (1.5 g.) was a red oil which g.c. analysis showed to consist mainly of the starting 1,2-cyclohexanediol diacetate with *trans*-2-chlorocyclohexyl acetate present as a minor component.

Hydrolysis of 2-Chlorocyclohexyl Acetate-O^{18} - Conversion to Cyclohexane Oxide-O^{18}

The distillate obtained above was added to 1.4 g. (25 mmoles.) of potassium hydroxide dissolved in 3 ml. of methanol and 12 ml. of water, and stirred at room temperature for 3 hrs. The reaction product was extracted with two 5-ml. portions of carbon tetrachloride. The solvent was removed by distillation to give a residue that was subjected to preparative g.c. (column A at 90°, 60 cc./min.). A clear, colorless liquid (338 mg.) identified as cyclohexene oxide by comparison of its infrared spectrum

(liquid film) with that of a standard was obtained. The product purity was estimated to be higher than 99% by g.c. analysis. The sample was analyzed for O^{18} content (p.67). The results are tabulated on p.97.

Hydrolysis of Recovered cis- and trans-1,2-Cyclohexanediol Diacetate-O^{18}

The red oil obtained above (p.65) was added to 1.7 g. (30 mmoles.) of potassium hydroxide dissolved in 3 ml. of methanol and 12 ml. of water, and stirred at room temperature for 3 hrs. The reaction product was extracted with five 10-ml. portions of chloroform. The solvent was removed (rotary evaporator) leaving a solid residue. After three recrystallizations from carbon tetrachloride, 117 mg. of a white solid was recovered. In the case of trans-1,2-cyclohexanediol-O^{18} it had a m.p. of 103.8-104.2° (lit.(108) m.p. 104°) while in the case of cis-1,2-cyclohexanediol-O^{18} the m.p. was 97-98° (lit.(109) m.p. 98°). The infrared spectra (KBr) of these compounds were identical to those of the corresponding standards. The products were analyzed for O^{18} content (p.67). The results are tabulated on p.97.

O-18 Analyses

A modification of the procedure of Rittenberg and Ponticorvo was utilized (78). Typically 5-15 mg. of the oxygen containing compound to be analyzed was added to 200 mg. of a mixture consisting of five parts by weight of mercuric chloride and one part of mercuric cyanide (commercial materials, mixed and vacuum dried at room temperature for 48 hrs.). This mixture was kept at -78° while being sealed in a break-seal tube that had been evacuated to a pressure of 10^{-5} mm on a vacuum rack. The sealed tube was heated in a muffle furnace at 475° for 1.5 hrs. The carbon dioxide formed was directly analyzed by a 60° sector field isotope-ratio mass spectrometer.* The O^{18} content was calculated from the following equation:

$$\frac{m_{46}}{m_{44} + m_{46}} \times 100 = \text{atom \% } O^{18}$$

where m_{44} and m_{46} are the intensities of the mass 44 and 46 peaks in carbon dioxide. The percent excess O^{18} was calculated by subtracting the O^{18} abundance in normal carbon dioxide as calculated from a standard carbon dioxide spectrum.

*Performed at the laboratory of Dr. D. Rittenberg, Columbia University, College of Physicians and Surgeons, New York City.

Reaction of Aluminum Dichloroacetate with (+)-S-2-Octyl Acetate

Using the apparatus described on p.52, an aluminum salt having the stoichiometry of aluminum dichloroacetate was prepared *in situ* by addition of 3.90 g. (29 mmoles.) of 1,2-ethanediol diacetate to 4.31 g. (29 mmoles.) of anhydrous aluminum chloride and heating of the mixture at 110° for 0.5 hr. (+)-S-2-Octyl acetate (p.32)(5.0 g., 29 mmoles.) was added to the aluminum dichloroacetate and the mixture was heated at 110° for 1 hr. The reaction was quenched and hydrolyzed as described on p.52. Vacuum distillation of the chloroform layer in a spinning band distilling column yielded 1.4 g. of a fraction containing 63% 2-chlorooctane and 27% 3-chlorooctane as determined by g.c. (column A at 58°, 45 cc./min.). The rotation of this fraction was $\alpha^{27}D$ -6.67 (1 dm., neat). The residue (0.74 g.) yielded 0.23 g. of (+)-S-2-octyl acetate by preparative g.c. (column B at 155°, 60 cc./min.). The collected material (96% pure by g.c.) had a specific rotation of $[\alpha]^{27}D$ +2.60° (c 1.37, chloroform).

The Competitive Reaction of 1,2-Ethanediol Diacetate and 1,3-Propanediol Diacetate with Aluminum Chloride

Using the apparatus described on p.52, 1.7 g. (11.8 mmoles.) of 1,2-ethanediol diacetate, 1.9 g.(11.8 mmoles.) of 1,3-propanediol diacetate, and anhydrous aluminum chloride (0.78 g., 5.8 mmoles.) were heated for three minutes at 94 $\pm$ 0.5°. Upon completion of the reaction the mixture was cooled to 0°C and analyzed directly by g.c. (column B at 165°, 60 cc./min.). An appropriate standard mixture was used to calculate the relative concentrations of the chloroacetate products.

Relative Reactivity of Acetate Esters with Aluminum Halides

(1) Competitive Reaction in the Absence of Solvent

A typical kinetic run was carried out in a similar manner to that described on p.57. E.g., anhydrous aluminum bromide 1.3 g.(4.9 mmoles.) was heated for 15 min. with 1.43 g. (11.0 mmoles.) of 2,2-dimethylpropyl acetate and 1.27 g. (10.9 mmoles.) of n-butyl acetate in an oil bath maintained at 115 ± 1°. The reaction was quenched by adding 10 ml. of n-hexane and 20 ml. of 0.5N hydrochloric acid. Internal standard(s) were then added and the n-hexane layer was analyzed quantitatively by g.c. (see pp. 58-59 for g.c. conditions). The relative reactivities of the acetates were calculated from equation 9 where Ao and Bo are the

$$\frac{K_A}{K_B} = \frac{\log \frac{A_o}{A}}{\log \frac{B_o}{B}} \qquad (9)$$

known initial concentrations of the two esters and A and B are their final respective concentrations as determined by g.c. analysis. The results are tabulated on p.119.

(2) Competitive Reaction in the Presence of Solvent

In a typical experiment, anhydrous aluminum bromide (1.2 g., 4.7 mmoles.), 1,6-hexanediol diacetate (1.62 g., 8.0 mmoles.), n-butyl acetate 1.28 g., 11 mmoles.), and 15 ml. of n-heptane were placed in a break-seal ampoule in the presence of a dry nitrogen atmosphere. The ampoule was sealed and the reaction allowed to proceed for 25 hrs. in an oil bath maintained at 95 ± 1°. The reaction was quenched by hydrolyzing with 10 ml. of 0.5N hydrochloric acid. Internal standard(s) were then added and the n-heptane layer was analyzed quantitatively by g.c. (see pp.58-59 for conditions). The relative reactivities were calculated using the formula shown on p.70. The results are tabulated on pp. 115 and 121.

Preparation of Aluminum Triacetate

Anhydrous aluminum bromide (3.0 g., 11.2 mmoles.) and 1,2-ethanediol diacetate (12.5 g., 85 mmoles.) were heated at 155-160° in the manner described on p.57. The formation of a brown precipitate was observed 5 min. after commencement of heating. Continued heating caused the disappearance of this solid. The reactants were heated for an additional 20 min. resulting in the formation of a precipitate similar to the first. This solid did not dissolve when heated for a longer period of time. The precipitate was filtered under a dry nitrogen atmosphere and washed with 50 ml. of dry benzene. The recovered solid was extracted for 40 hrs. with n-hexane in a Soxhlet apparatus that was protected with a drying tube. The solid material was then dried in vacuum for 5 hrs. at room temperature. The solid so obtained was white in color. Ir (p.78) (nujol mull): OH absent, 1655(m), 1600(m), 1040(w), 1020 cm^{-1}(w); (lit.(26) ir (mull)): OH absent, 1595(s), 1040(w), 1017(w), 989 cm^{-1}(vw). Anal. Calcd. for $C_8H_8AlO_8$: C,35.30; H, 4.41; Al, 13.22. Found: C,32.25; H,4.23; Al,15.01; Br,1.69.

Reaction of Zinc Chloride and Hydrogen Chloride with 1,2-Ethanediol Diacetate

A 50 ml. three-necked flask was equipped with two condensers and a mechanical stirrer. The flask was charged with 0.133 g. (1.0 mmoles.) of anhydrous zinc chloride and 3.5 g. (25 mmoles.) of 1,2-ethanediol diacetate. Hydrogen chloride gas with a flow rate of 60 cc./min. was passed into the flask. The exit gases were passed through two traps cooled to -78°. The reaction mixture was heated and stirred at 161 ± 3° for 1 hr. Upon completion of the reaction, the gas flow was stopped and the flask cooled to room temperature. An internal standard, 1-pentyl acetate (0.085 g., 0.65 mmoles.) was added and g.c. analysis performed (column A at 140°, 45 cc./min.). The results of this reaction are discussed on p. 98.

The Reaction of Zinc Chloride and Hydrogen Chloride with 1,2-Ethanediol and 1,3-Propanediol Diacetates-O^{18}

The reaction was performed as described on p.73. Anhydrous zinc chloride and HCl gas were heated with 1,2-ethanediol diacetate-O^{18} (p.50) or 1,3-propanediol diacetate-O^{18} (p.50) at 150-155° for 12 min. G.c. analysis in each case showed that the reaction had proceeded to 75-80% completion. The hydrolysis is similar to that described on p.61. Each distillate and residue was prepared for O^{18} analysis as discussed on pp.61-63. 1,3-Propanediol diacetate, 3-chloropropanol, 1,3-propanediol dibenzoate and 1,2-ethanediol dibenzoate were analyzed for O^{18} as described on p.67. 1,2-Ethanediol diacetate and 2-chloroethanol were analyzed for O^{18} by Isotopes Inc. of Westwood, New Jersey. The results are tabulated on pp. 99-100.

Reaction of Zinc Chloride with 1,3-Propanediol Diacetate-O^{18}

The reaction and hydrolysis were performed as described on pp.61. Anhydrous zinc chloride (6.6 g., 48.3 mmoles.) and 7.7 g.(48.0 mmoles.) of 1,3-propanediol diacetate-O^{18} were heated for 6.5 hrs. at 153 $\pm$ 2°. G.c. analysis (column A at 175°, 45 cc./min.) indicated a yield of 12% for the 3-chloropropyl acetate product. The chloroacetate was converted to 3-chloropropanol as described on pp.61-62, and analyzed for O^{18} content (p.67). The results are tabulated on p. 101.

SPECTRA

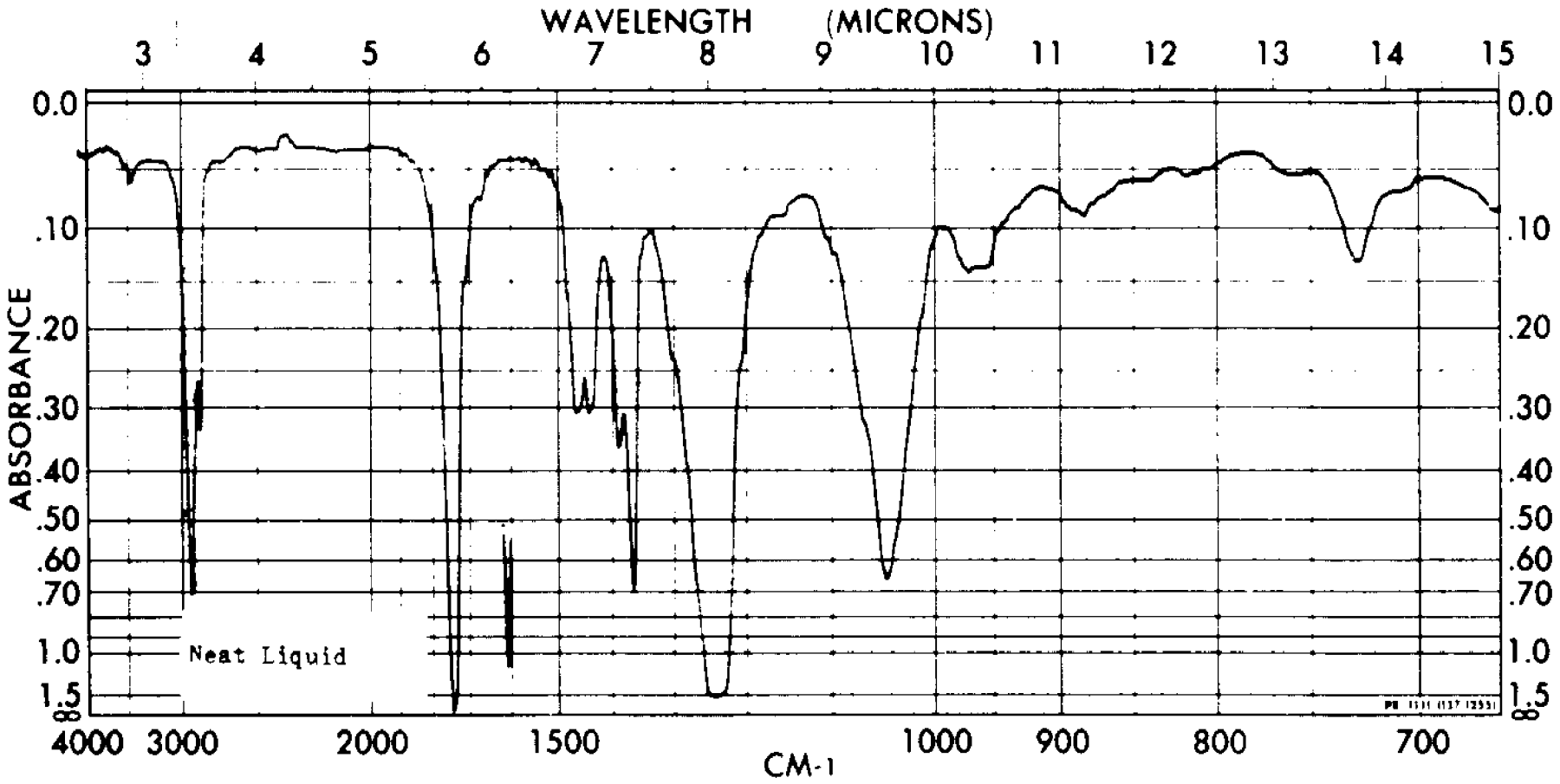


Fig. 1. Infrared Spectrum of n-bromohexyl acetate

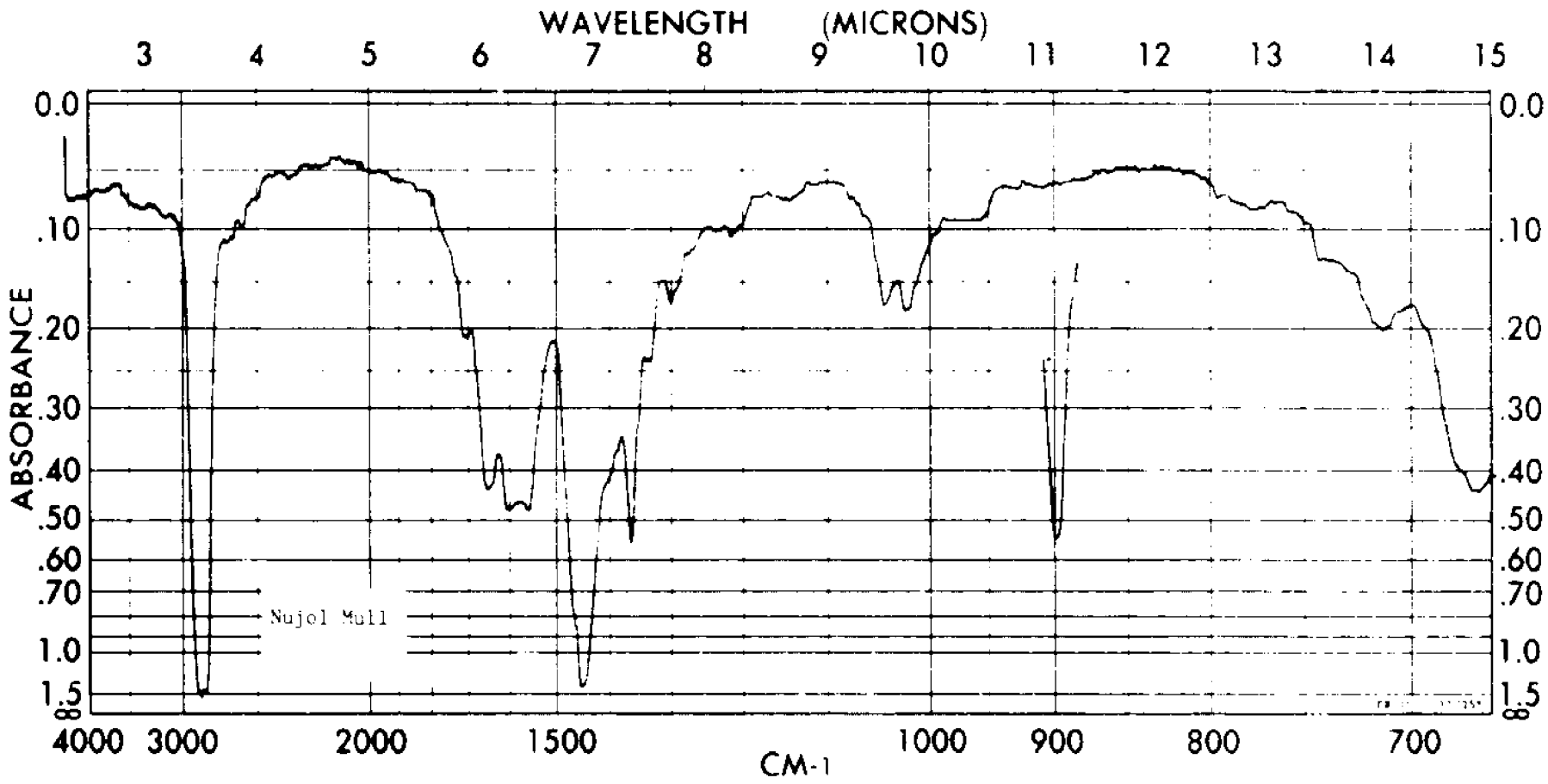


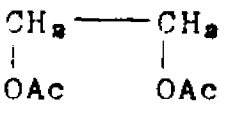
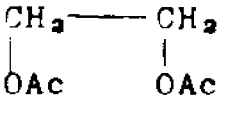
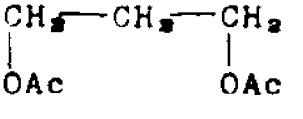
Fig. 2. Infrared Spectrum of Aluminum Triacetate

Results

A) Reaction of Halogen-Containing Lewis Acids with 1,2-and 1,3-Polyol Acetates

An investigation of the reaction of aluminum chloride with 1,2-ethanediol diacetate and 1,3-propanediol diacetate revealed the corresponding primary chloroacetates, 2-chloroethyl acetate and 3-chloropropyl acetate, respectively as the sole products of the reaction (Table III).

Table III: Reaction of Aluminum Chloride with 1,2-and 1,3-Polyol Acetates[a]

Acetate	Acetate/$AlCl_3$	Temp. °C	% Yield Chloroacetate[b]	% Recovered Acetate
	2:1	152 ± 2	98	3
	3:1	152 ± 2	95	35
	3.5:1	155 ± 2	91	—[c]

[a]Heated for one hour

[b]Based on stoichiometry of equation 2 (page 7)

[c]Not determined

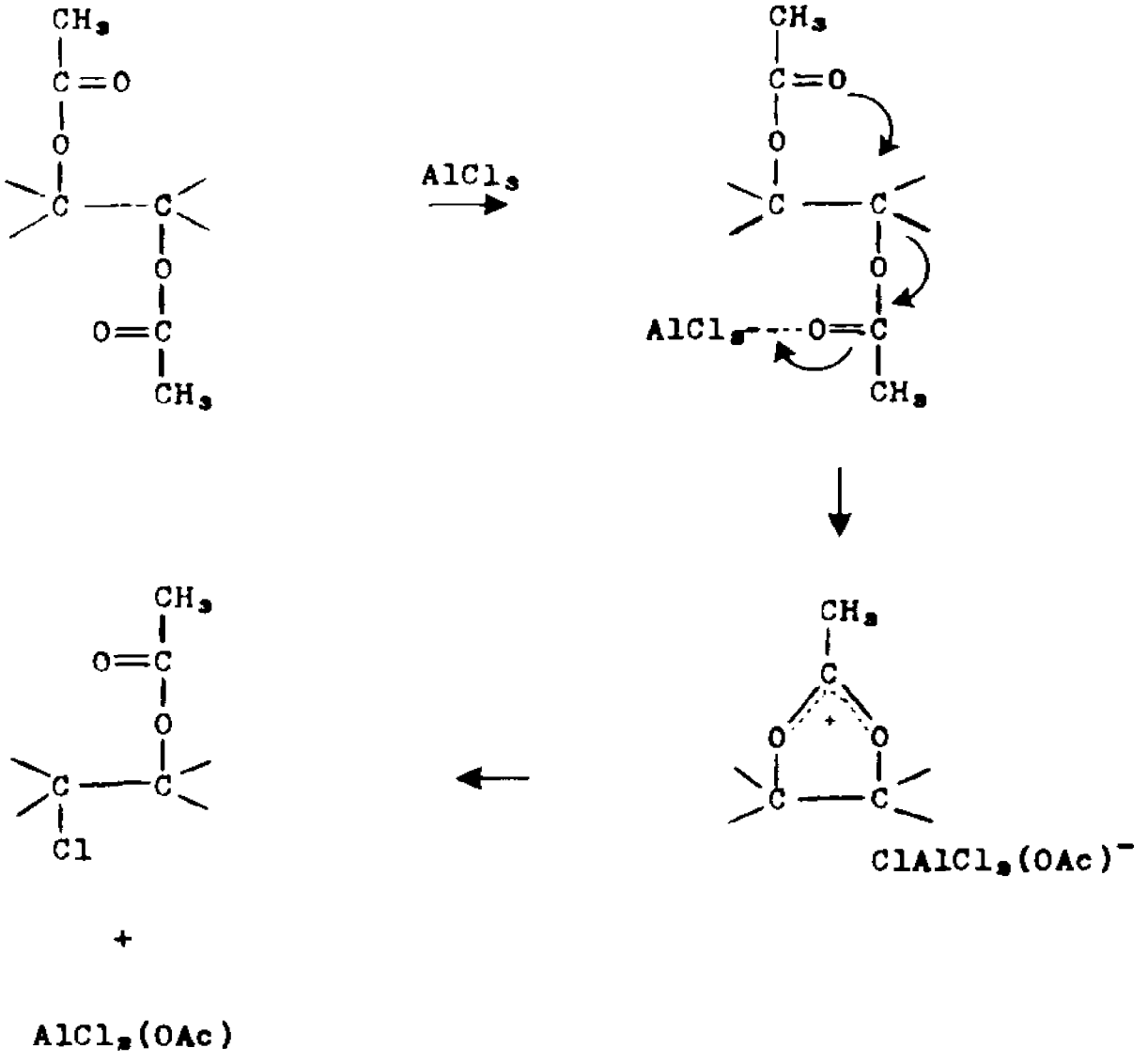
The previously proposed stoichiometry of these reactions (equations 2-4, p.7) was confirmed by the observation that one mole of aluminum chloride could react with no more than two moles of diacetate (Table III, p.79). The apparent need for the interaction of acetoxy groups with one another was reflected in the failure of 2-chloroethyl acetate to give any appreciable product as a result of its reaction with aluminum chloride. Heating 2-chloroethyl acetate at 153 $\pm$ 2° for one hour led to only a 6% yield of 1,2-dichloroethane. It is unlikely that replacement of acetoxy by halogen on the ester could sufficiently reduce the rate of further replacement to account for the observed results, as both acetoxy and chlorine are electron withdrawing groups that operate inductively with similar magnitudes (90). Furthermore, the addition of an inert solvent, such as carbon tetrachloride apparently had no influence on the mechanistic pathway of the displacement. A mixture of ethanediol diacetate and aluminum chloride in a 2:1 molar ratio, was diluted approximately 1:1 with carbon tetrachloride and refluxed for one hour, the only product of the reaction being the 2-chloroethyl acetate. Introduction of minute quantities of water ($<$ 1.5%) into the 1,2-ethanediol diacetate and aluminum chloride reaction mixture resulted in no new products, the only observable effect being a reduction in the yield of the 2-chloroethyl acetate,

probably as a result of the hydrolysis of aluminum chloride.

The neighboring group participation mechanism involving the formation of an acetoxonium ion intermediate was previously suggested by Wilen and Vanderhoek (97,106) as outlined in Scheme VII, (p.82) in order to account for the resistance of one acetoxy group to displacement.

A substantial body of experimental evidence demonstrates the fact that Lewis acids complex with the carbonyl oxygen of a carbalkoxy group. Infrared spectra of 1:1 complexes of aluminum chloride, as well as other halogen-containing Lewis acids, with ethyl and propyl acetate show a significant decrease in the carbonyl stretching frequency relative to the free ligand (13,55). The coordination complex of zinc chloride with pentaerythritol tetraacetate also shows significant shifts in the carbonyl stretching frequency relative to the free acetate (100). Both of these types of shifts are interpreted as being due to coordination at the carbonyl oxygen of esters with attendant decrease in double bond character. It is clear then that the first step in all reactions of esters with halogen-containing Lewis acids is complex formation, i.e., acid-base reaction at the carbonyl oxygen. The weakening of the alkyl C-O bond as a result of complexing leading to the formation of an ion pair is thus a key step in the displacement of acyloxy groups by halogen.

Scheme VII



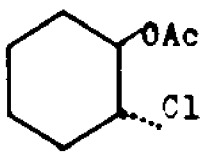
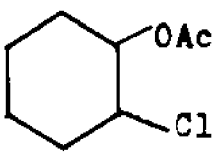
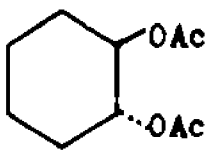
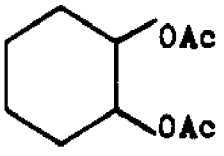
An investigation of the reaction of aluminum chloride with cis-and trans-1,2-cyclohexanediol diacetates was undertaken in order to obtain kinetic and stereochemical evidence in support of a neighboring group participation mechanism. A competitive reaction between trans-1,2-cyclohexanediol diacetate and cyclohexyl acetate at 156° shows the monoacetate to be 8.3 times more reactive than the trans compound reflecting the 2-acetoxy group's ability to inductively destabilize the carbonium ion intermediate. However, the competitive reaction of aluminum chloride with cis-and trans-1,2-cyclohexanediol diacetates, where the inductive effect difference is minimized, reveals the trans isomer to be faster by a factor of only 3.5 at 156°. This relative rate however, was not indicative of the anchimeric assistance which normally accompanies acetoxy neighboring group participation, as solvolytic reactions passing through a similar intermediate have shown rate enhancements greater than 500 at 75° (113).

The major product of the reaction of both of these diacetates with aluminum chloride was trans-2-chlorocyclohexyl acetate with no cis isomer being detectable under the analytical conditions employed. This finding offered no clear stereochemical evidence for acetoxonium ion intervention in the trans isomer. The results of these reactions are summarized in Tables IV and V

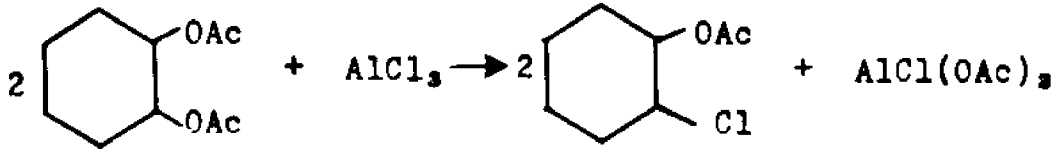
(pp.85 and 86, respectively).

The possibility of the isomerization of the cis diacetate to the trans isomer followed by its conversion to the trans-2-chlorocyclohexyl acetate was discounted as the data in Table V (p.86) revealed the presence of less than one percent trans-cyclohexanediol diacetate. The data in Table IV (p.85) and the measured relative rate of reaction of the two esters require that trans-diacetate would have accumulated in the reaction mixture beyond the minimum detectable yield level had such an isomerization taken place. This conclusion is supported by O^{18} labeling data presented below. In addition, the absence of the interconversion of the cis-and trans-2-chlorocyclohexyl acetates in the presence of aluminum chloride under the reaction conditions was demonstrated (Table VI, p.87). These reactions revealed cis-and trans-1,2-dichlorocyclohexane to be products along with numerous unidentified minor components. The predominance of the trans dichloride as a product in the trans-2-chlorocyclohexyl acetate reaction may be reflective of the possible neighboring group participation by the chlorine atom, with the resulting formation of a chloronium ion intermediate (74).

Table IV: Reaction of Aluminum Chloride with Trans-1,2-Cyclohexanediol Diacetate[a,b]

Molar Ratio[d]	Temp. °C				
3.2:1	157 ± 2	60%	<4%[c]	11%	<1%
2.1:1	157 ± 2	50%	<3%[c]	16%	<1%
2.0:1	113 ± 2	43%	<3%[c]	27%	<1%

[a]Yields are based upon stoichiometry of the following equation

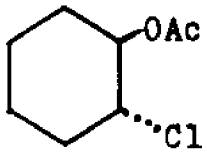
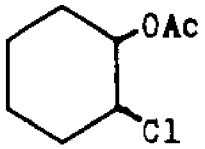
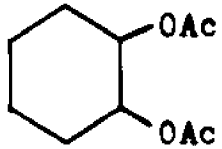
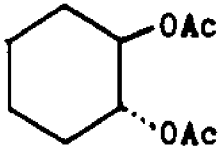


[b]All reactions were heated for one hour

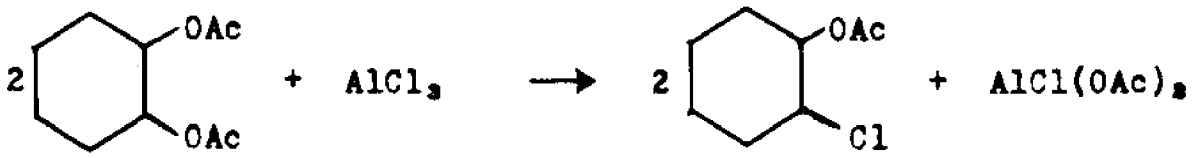
[c]Minimum detectable yield

[d]Molar ratio of ester to aluminum chloride

Table V: Reaction of Aluminum Chloride with Cis-1,2-Cyclohexanediol Diacetate[a,b]

Molar Ratio[d]	Temp. °C				
2.1:1	158 ± 3	21%	< 1.5%[c]	39%	< 1%
2.3:1	113 ± 3	14%	< 1%[c]	50%	< 1%

[a]Yield based on stoichiometry of the following equation:

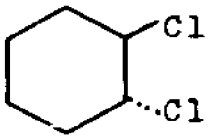
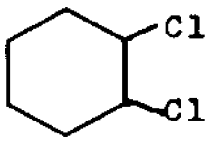
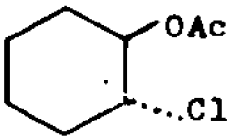
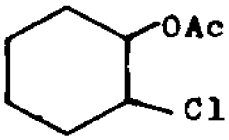
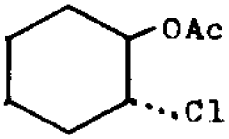
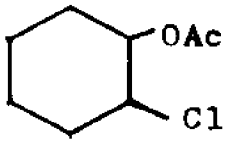


[b]Heated for one hour

[c]Minimum detectable yield

[d]Molar ratio of ester to aluminum chloride

Table VI: Reaction of Aluminum Chloride with Cis-and Trans-2-Chlorocyclohexyl Acetate[a]

Acetate	Molar Ratio[b]				
	2.0:1	16%	2%	29%	<2%[c]
	2.1:1	4%	2%	<2%[c]	29%

[a]Heated for one hour at 156 ± 2°

[b]Molar ratio of ester to aluminum chloride

[c]Minimum detectable yield

Since the proposed mechanism involved the formation of an acetoxonium ion intermediate, an oxygen-18 label study was adopted as a means of further investigating the mechanism of the reaction of Lewis acids with polyol acetates. If a polyol diacetate containing a labelled carbonyl oxygen were to pass through a perfectly symmetrical acetoxonium ion intermediate, and if internal return is neglected, a 25% incorporation of the O^{18} would be expected in the alkyl oxygen position of the final

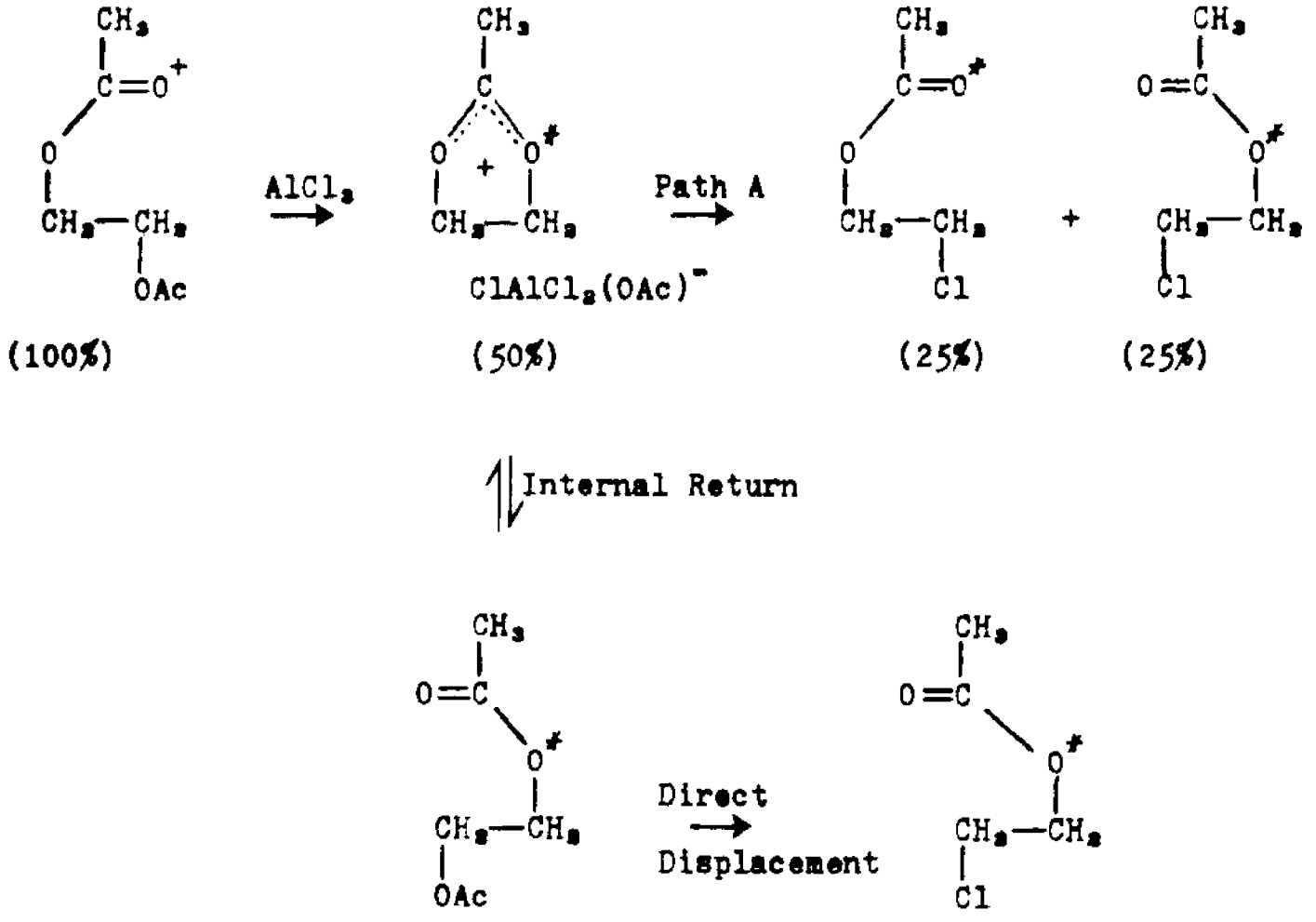
product as illustrated by Path A in Scheme VIII (p.89). Acetoxonium ion pairs however, have been known to reform the starting material by undergoing internal return (115). If this process were to occur with a labelled diacetate in its reaction with a Lewis acid the outcome would be to scramble the labelled oxygen before a displacement had actually occurred, thus making it impossible to determine whether the labelled alkyl oxygen resulted from internal return and subsequent unassisted direct displacement or assisted displacement (Path A) as outlined in Scheme VIII (p.89). In order to measure the extent to which scrambling had occurred in the starting material, the reactions of labelled polyol acetates were in most instances not run to completion. This permitted the recovery of the starting polyol acetate and the subsequent analysis of its alkyl oxygen for O^{18} content. The extent of scrambling was then taken into account in the calculation of the minimum value of acetoxonium ion formation by assuming internal return to be an infinitely fast process. The following equation was applied in these calculations:

$$\frac{A}{4} N + \frac{B}{4} N + \frac{B}{2} (1-N) = C \qquad (10)$$

where

1) A equals the atom percent excess O^{18} in the diacetate labelled only at the carbonyl oxygen

Scheme VIII


AlCl3
Path A
ClAlCl2(OAc)⁻
(100%)
(50%)
(25%)
(25%)
Internal Return
Direct
Displacement

multiplied by the number of oxygens in the molecule.

2) B equals the atom percent excess O^{18} in the diacetate labelled only at the alkyl oxygen multiplied by the number of oxygens in the molecule.

3) C equals the atom percent excess O^{18} of the alkyl oxygen of the final product multiplied by the number of oxygens in the molecule.

4) N x 100 equals the minimum percent of acetoxonium ion formation.

The derivation of this relationship stems from the need to adjust the maximum percent of acetoxonium ion formation, N^1, for scrambling through internal return and subsequent direct displacement.

$$\frac{A + B}{4} N^1 = C \qquad (11)$$

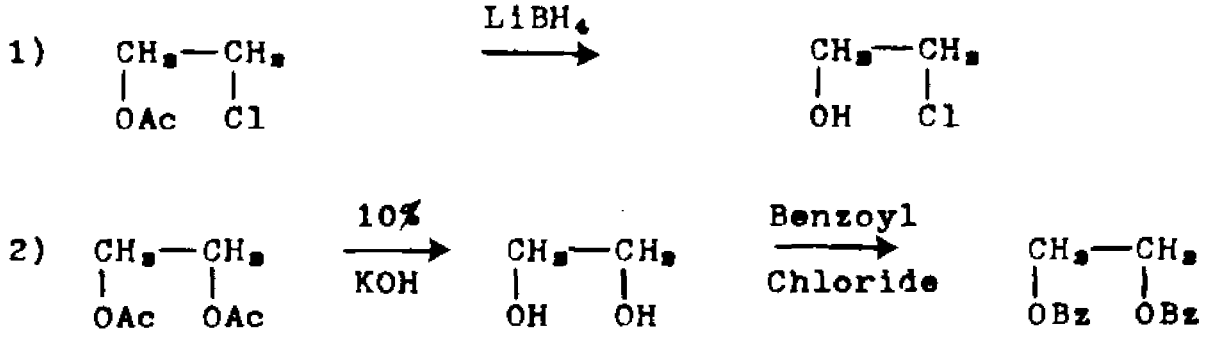
The third term in equation 10 represents the percent of diacetate scrambled by internal return and undergoing direct displacement to give a labelled alkyl oxygen.

The appropriately labelled polyol acetates were prepared by acetylating the corresponding polyol with acetyl chloride-O^{18}. The latter was prepared by hydrolysis of unlabelled acetyl chloride with 3.8-5% atom percent excess water O^{18}, followed by treatment with thionyl chloride to regenerate acetyl chloride. All labelled compounds were combusted to carbon dioxide

according to the modified procedure of Rittenberg and Ponticorvo (78) and analyzed for O^{18} content by mass spectroscopy (p.67). The results were assumed to have a maximum error of 3% (93).

The first system to be studied in this manner was that of 1,2-ethanediol diacetate-O^{18} and aluminum chloride. The reaction of the labelled diacetate was permitted to go to 80% of completion at 104 ± 2°. The reaction mixture was hydrolyzed, the product and unreacted starting material were separated by distillation and subsequently treated as outlined in Scheme IX.

Scheme IX



The starting diacetate, the recovered chlorohydrin, and the dibenzoate were combusted to carbon dioxide and analyzed for O^{18} content. The results of these analyses are summarized in Table VII (p.92).

Table VII: O^{18} Analysis in the 1,2-Ethanediol Diacetate Reaction with $AlCl_3$ (104 ± 2°)[a,b]

$CH_2(OAc)-CH_2(OAc)$	$CH_2(OH)-CH_2Cl$	$CH_2(OBz)-CH_2(OBz)$
1.17 ± 0.2%	1.13 ± 0.01%	0.159 ± 0.08%

[a]Results calculated in atom % excess

[b]Results represent average values and average deviations of two or more determinations.

If a perfectly symmetrical acetoxonium ion intermediate had been formed, a 25% incorporation of O^{18} would have been expected for the chlorohydrin (Scheme VIII, p.89). An experimental value of 24.2% incorporation was found. Thus a maximum of 96.6% of the 2-chloroethyl acetate was formed through an acetoxonium ion intermediate. The O^{18} content of the dibenzoate showed that scrambling of the starting diacetate had occurred to the extent of 27.6% (Table VII). In order to correct for the possibility of a straight displacement on a scrambled diacetate equation 10 was used to calculate the minimum extent of neighboring group participation. A minimum value of 95.3% was calculated for neighboring group participation with the true value evidently lying somewhere between 95.3% and the previously calculated maximum, 96.6%.

The possible intervention of a six-membered

acetoxonium ion was investigated by examining the aluminum chloride - 1,3-propanediol diacetate-O^{18} reaction. The reaction was carried out to 65% completion at 106 ± 2°. O^{18} Analysis of the starting diacetate and the recovered 3-chloroethanol revealed a maximum of 97.3% acetoxonium ion formation (Table VIII, p.93).

Table VIII: O^{18} Analysis of the 1,3-Propanediol Diacetate Reaction with $AlCl_3$ (106 ± 2°)[a,b]

$CH_2(OAc)-CH_2-CH_2(OAc)$	$CH_2(OH)-CH_2-CH_2Cl$
0.660 ± 0.001%	0.642 ± 0.002%

[a]Results are calculated in atom % excess

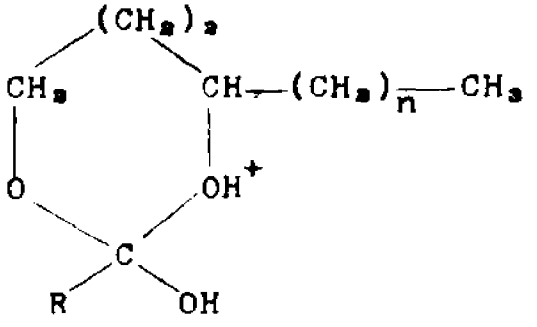
[b]Results represent average value and average deviations of two determinations

The major mechanistic pathway in the reaction of 1,2-ethanediol diacetate and 1,3-propanediol diacetate with aluminum chloride was thus demonstrated to proceed through the intervention of an acetoxonium ion intermediate. The simplicity and cleanliness of the substitution reactions of the two and three carbon diacetates with aluminum chloride suggested a relative

rate study to provide information about the relative stability of five-membered vs. six-membered unsubstituted acetoxonium ions. The two diacetates were heated with aluminum chloride at 94 ± 0.5° for three minutes allowing only 80% of the aluminum chloride to react. The concentrations of the two products, 2-chloroethyl acetate and 3-chloropropyl acetate, were determined by gas chromatography, and this was directly related to their relative rates of formation. As a result it was concluded, assuming that acetoxonium ion formation is rate determining, that the relative rate of formation of a five-membered to a six-membered acetoxonium ion at 94 ± 0.5° was 5.0:1.

The competitive reaction of 1,3-propanediol diacetate and 1,4-butanediol diacetate with aluminum chloride was carried out in a similar manner in order to obtain relative rate data relating to the possible existence of a 7-membered acetoxonium ion. At 94 ± 0.5° it was determined that the 3-chloropropyl acetate product formed at a rate 43 times faster than 4-chlorobutyl acetate. In a separate experiment the reaction of aluminum chloride with a mixture of 3-chloropropyl acetate and 4-chlorobutyl acetate confirmed their stability under the reaction conditions. Whether the 4-chlorobutyl acetate product involved the formation of a 7-membered acetoxonium ion is not known. However, a relative rate of 215 for the

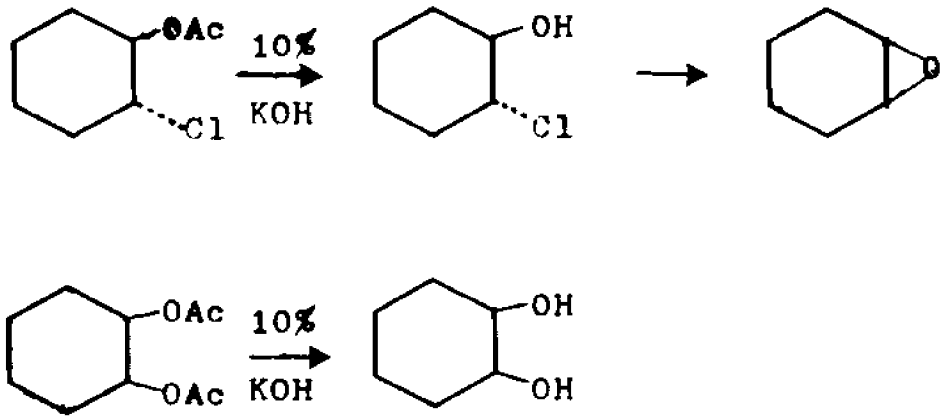
formation of 2-chloroethyl acetate, through a 5-membered acetoxonium ion, compared to 4-chlorobutyl acetate is a clear indication of anchimeric assistance. No evidence has yet been presented for the existence of a seven-membered acetoxonium ion. Derbesy and Naudet (18) have suggested the existence of a seven-membered orthoester (XV) in their investigation of the isomerization of long-chained hydroxy esters, however.



XV

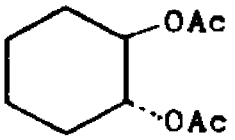
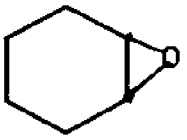
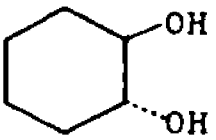
As the previously obtained kinetic and stereochemical evidence was unsuccessful in fully elucidating the mechanism of the reaction of aluminum chloride with cis-and trans-1,2-cyclohexanediol diacetate, the reactions of aluminum chloride with each of these polyol esters labelled with O^{18} at a carbonyl oxygen were investigated. After being heated at 110-114° for one hour, each of the reaction mixtures was hydrolyzed with 0.5N hydrochloric acid, the trans-2-chlorocyclohexyl acetate product and the starting diacetate recovered by distillation, and each treated with 10% aqueous potassium hydroxide (Scheme X)(p.96).

Scheme X



The reaction of the trans-1,2-cyclohexanediol diacetate-O^{18} was carried out at 110 ± 3° to yield 43% trans-2-chlorocyclohexyl acetate and 27% unreacted starting material. The cis-1,2-cyclohexanediol diacetate-O^{18} was heated at 112 ± 2° with aluminum chloride to yield 14% trans-2-chlorocyclohexyl acetate and 50% unreacted starting material. The O^{18} combustion data is summarized in Tables IX and X (p.97).

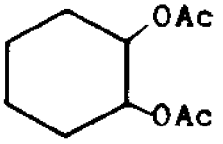
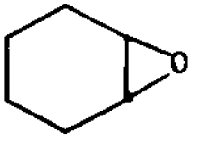
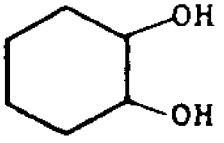
Table IX: O^{18} Analysis in the Trans-1,2-Cyclohexanediol Diacetate Reactions with $AlCl_3$ (110 ± 3°)[a,b]

		
0.837 ± 0.22%	0.730 ± 0.033%	0.252 ± 0.012%

[a]Results calculated in atom % excess

[b]Results represent an average of two or more determinations

Table X: O^{18} Analysis in the Cis-1,2-Cyclohexanediol Diacetate Reactions with $AlCl_3$ (112 ± 2°)[a,b]

		
1.19 ± 0.000%	0.052 ± 0.012%	0.024 ± 0.019%

[a]Results are calculated in atom % excess

[b]Results represent an average of two or more determinations

The cyclohexene oxide recovered from the trans-1,2-cyclohexanediol diacetate-O^{18} reaction gave an experimental value of 21.8% O^{18} incorporation. This corresponds to a maximum of 87.2% acetoxonium ion formation. As the recovered trans-1,2-cyclohexanediol showed scrambling

to the extent of 28.6%, the minimum value of neighboring group participation could be calculated from equation 10 where it is assumed that scrambling is an infinitely faster process than any other competing reaction. A minimum value of 81.8% was thus calculated. In the cis-1,2-cyclohexanediol diacetate-O^{18} system, 4.4% acetoxonium ion intervention was observed and only 2.2% scrambling was found to have occurred.

Previously investigations of the reaction of zinc chloride and hydrogen chloride with 1,3-diol acetates (100,101) ignored the possibility of neighboring group participation in the explanation of the enhanced rate of removal of the first acetoxy group (see Table I, p.14). An examination of the reaction of 1,2-ethanediol diacetate with zinc chloride-HCl further confirmed the resistance of one carboxylate group to displacement; after being heated for one hour at 161 $\pm$ 3° 95% 2-chloroethyl acetate was obtained and less than 0.2% 1,2-dichloroethane recovered.

An O^{18} labeling study of the zinc chloride-hydrogen chloride reaction with 1,2-ethanediol diacetate-O^{18} and 1,3-propanediol diacetate-O^{18} was undertaken for the purpose of determining the extent of possible acetoxonium ion intervention. The reactions were allowed to react to approximately 80% of completion before being quenched. The reaction mixtures were hydrolyzed, the products

isolated by distillation, and subsequently treated as outlined in Scheme IX, p.91. The starting diacetates as well as the corresponding chlorohydrins and dibenzoates were combusted to carbon dioxide and analyzed for O^{18} content.

An experimental value of 17.5% O^{18} incorporation was obtained from the 2-chloroethanol (Table XI). This represents a maximum value of 70.1% for acetoxonium ion intervention. The dibenzoate analysis showed scrambling to have occurred to the extent of 51.2%. Equation 10 was used to calculate the minimum extent of acetoxonium ion intervention during the formation of 2-chloroethyl acetate. The value found as a minimum was 38.6%. The actual value for neighboring group participation thus lies somewhere between 38.6 and 70.1%.

Table XI: O^{18} Analysis in the 1,2-Ethanediol Diacetate Reaction with $ZnCl_2$-HCl (153 ± 2°)[a]

$CH_2(OAc)-CH_2(OAc)$	$CH_2(OH)-CH_2Cl$	$CH_2(OBz)-CH_2(OBz)$
0.828 ± 0.018%[b]	0.580 ± 0.027%[b]	0.212%[c]

[a]Results calculated in atom % excess

[b]Represents average values and average deviations of two or more determinations

[c]One Determination

A similar study involving 1,3-propanediol diacetate-O^{18} with zinc chloride-hydrogen chloride showed only 9.2% O^{18} incorporation in the 3-chloropropanol (Table XII). This corresponds to a maximum value of 36.7% neighboring group participation. The O^{18} content of the dibenzoate indicated scrambling had occurred to the extent of only 12.4%. A minimum value of 27.8% acetoxonium ion intervention can thus be calculated from equation 10 (p.88).

The O^{18} labeling data from this study are summarized in Table XII.

Table XII: O^{18} Analysis in the 1,3-Propanediol Diacetate Reaction with $ZnCl_2$-HCl (151 ± 2°)[a]

$CH_2(OAc)-CH_2-CH_2(OAc)$	$CH_2(OH)-CH_2-CH_2Cl$	$CH_2(OBz)-CH_2-CH_2(OBz)$
0.894 ± 0.03%[b]	0.328 ± 0.022%[b]	0.055%[c]

[a] Results are calculated in atom % excess

[b] Represents average values and average deviations of two or more determinations

[c] One determination

In order to determine what role, if any, the protonic acid has in these displacements, the previous results were compared to data obtained from the reaction of 1,3-propanediol diacetate-O^{18} with zinc chloride in the absence of hydrogen chloride. After 6.5 hours of heating at 153 ± 2° only 12% 3-chloropropyl acetate was recovered, this compared to a yield of 85% for 3-chloropropyl acetate obtained from heating 1,3-propanediol diacetate with zinc chloride-HCl at 151 ± 2° for 17 minutes. The O^{18} data are summarized in Table XIII.

Table XIII: O^{18} Analysis in the 1,3-Propanediol Diacetate Reaction with $ZnCl_2$ (152 ± 2°)[a,b]

$CH_2(OH)-CH_2-CH_2(OAc)$	$CH_2(OH)-CH_2-CH_2Cl$
0.660 ± 0.001%	0.621 ± 0.007%

[a] Results are calculated in atom % excess

[b] Average values and average deviations from two determinations

The 3-chloropropanol product incorporated 23.5% of the O^{18} label, which corresponds to a maximum value of 94.1% acetoxonium ion intervention. This represents a two and one-half fold increase over that found in the

analogous zinc chloride-hydrogen chloride-1,3-propanediol diacetate system (Table XII, p.100). Also, the extent of neighboring group participation involving $ZnCl_2$ and $AlCl_3$ (Table VIII, p.93) is not significantly different.

The reaction of aluminum bromide with 1,2-ethanediol diacetate has been reported as yielding only 1,2-dibromoethane (equation 5, p.10), while a similar reaction with 2,2-dimethyl-1,3-propanediol diacetate was claimed to yield only the product of monosubstitution, 2,2-dimethyl-3-bromopropyl acetate (equation 7, p.10) (47). A reinvestigation of these reactions was undertaken in order to obtain both qualitative and quantitative gas chromatographic data for comparison with the aluminum chloride studies. Contrary to the findings of Jedlinski and Paprotny (47), 1,2-ethanediol diacetate yielded both 1,2-dibromoethane and 2-bromoethyl acetate as products (Table XIV, p.103). If these reactions had stopped with the formation of the aluminum bromodiacetate salt in analogy to the aluminum chloride reactions (equations 2-4 (p.7), the extent of reaction, as defined in Table XIV (p.103), would have had a maximum value of 66.6%. Instead, the observed values exceeded this figure. The reaction stoichiometry is clearly different - at least in part - with $AlCl_3$ and $AlBr_3$. In the latter case, the reaction must be proceeding to the aluminum triacetate stage. Indeed, unlike the previously studied aluminum

Table XIV: Products Formed in the Reaction of 1,2-Ethanediol Diacetate with $AlBr_3$

Molar Ratio[a]	Time Hr.	Temp. °C	$\frac{CH_2-CH_2}{Br\ \ Br}$ / $AlBr_3$	$\frac{CH_2-CH_2}{Br\ \ OAc}$ / $AlBr_3$	Recovered Acetate	Extent of Reaction[b]
2:1	1	157 ± 2	0.37	1.33	4%	69%
2:1	1	150 ± 2	0.36	1.58	6%	77%
2:1	1	155 ± 2	0.43	1.37	5%	75%
2:1	1	158 ± 2	0.53	1.38	4%	81%
2:1	1	155 ± 2	0.46	1.47	4%	80%
3:1	0.5	155 ± 2	0.27	1.67	25%	74%
3:1	0.5	154 ± 2	0.26	1.58	28%	70%

[a]Molar ratio of ester to aluminum bromide

[b]The ratio of the number of moles of displaced acetoxy groups to the initial number of equivalents of aluminum bromide, multiplied by 100.

chloride systems, a solid material believed to be aluminum triacetate was observed to precipitate from solution near the completion of the reaction. Isolation and analysis of this material was attempted (p.118) in order to identify it. This is discussed on page 118.

As with aluminum chloride and zinc chloride, infrared studies of the complexes of aluminum bromide with various esters have shown coordination with the carbonyl oxygen (13,15). It is not unreasonable to assume that the displacement of the first acetoxy in 1,2-ethanediol diacetate, as in previous reactions with Lewis acids, proceeds with acetoxonium ion intervention. The possibility of bromonium ion intervention does, however, exist for the displacement of the second acetoxy group. Halonium ion intervention is known to be much more important a process with bromine than with chlorine (15). The competitiveness of these two displacements was illustrated by the formation of some 1,2-dibromoethane even when 1,2-ethanediol diacetate and aluminum bromide react in a 3:1 molar ratio. In accord with this finding, kinetic studies of the acetolysis of trans-2-acetoxycyclohexyl brosylate and trans-2-bromocyclohexyl brosylate show these two neighboring group assisted displacements to have a relative rate of 2:1, respectively (113).

In contrast to the results summarized in Table XIV

(p.103), 2,2-dimethyl-1,3-propanediol diacetate gave only the 2,2-dimethyl-3-bromopropyl acetate product (Table XV, p.106), as previously reported (equation 7, p.10). If the unaccounted for starting diacetate is assigned to the formation of subsequently destroyed dibromide product the maximum extent of reaction can be calculated to be 59-60%.

Since the maximum extent of reaction was not found to exceed 66.6% it was reasoned that the reaction could not have gone beyond the aluminum bromodiacetate stage in this case. Steric inhibition to complexing by aluminum bromodiacetate would be the likely cause of this effect. A similar example of this type of steric hindrance is the observed inability of zinc chloride to coordinate with the carbonyl oxygen of the monoester pentaerythritol trichloroacetate at 200° (100), while otherwise it has been shown that zinc chloride does coordinate at the carbonyl oxygen of simple esters (13,55). In general it seems that Lewis acids have great difficulty in complexing with neopentyl-type acetates; suggestive of this it was observed that at 150° aluminum bromide dissolved in 2,2-dimethyl-1,3-propanediol diacetate with difficulty over a period of fifteen minutes. This is in contrast to the almost instantaneous solution of the aluminum bromide in normal (unbranched) diacetates under similar conditions.

Table XV: Products Formed in the Reaction of 2,2-Dimethyl-1,3-Propanediol Diacetate with $AlBr_3$[a]

Molar Ratio	Temp. °C	$\frac{AcO-CH_2-C(CH_3)_2-CH_2-Br}{AlBr_3}$	Recovered Acetate[b]	Maximum Extent of Reaction
2:1	156 ± 3	1.43	20%	59%
2:1	154 ± 3	1.39	20%	60%
1:1	156 ± 3	0.84	1%	-
1:1	154 ± 2	0.63	3.5%	-
1:1	155 ± 2	0.73	< 1%	-

[a]Heated for one hour

[b]No rearranged starting material found

Initially, the failure to find any 2,2-dimethyl-1,3-dibromopropane in the reaction product of the aluminum bromide-2,2-dimethyl-1,3-propanediol diacetate system was thought reasonable on the basis of similar evidence for the absence of dihalides in the analogous aluminum chloride reaction series (equations 2-4,p.7). However, further investigation revealed that this expected product, 2,2-dimethyl-1,3-dibromopropane, was completely destroyed by aluminum bromide at 153 $\pm$ 2° in one hour. No starting material was recovered in this reaction and at the same time no volatile products were observed, by gas chromatographic analysis. Nmr analysis of the recovered reaction mixture revealed a polymeric product to be the only detectable one. It is thus possible that 2,2-dimethyl-3-bromopropyl acetate may have reacted with aluminum bromide or with aluminum bromodiacetate resulting in a cationic intermediate that was polymerized before forming the expected dibromide product.

When this reaction was repeated with a mixture of the dibromoneopentane and the acetoxybromoneopentane, the former was found to have survived under the reaction conditions, thus demonstrating the apparent inability of the cationic intermediate to form in the presence of aluminum bromide without becoming polymerized. The hypothesis of carbonium ion formation in the reaction

of acetoxybromoneopentane with aluminum bromide was further supported by gas chromatographic examination of the reaction mixture of 2,2-dimethylpropyl acetate with aluminum bromide, which were heated together at 110° for one hour. The chromatogram showed that 17% of the starting material was consumed. No volatile products were detected. In the presence of aluminum bromide alone, both bromo-2,2-dimethylpropane and a likely rearrangement product, 2-bromo-2-methylbutane, were found to completely polymerize, no product(s) being detectable by gas chromatography. It was also demonstrated that bromo-neopentane could and did survive under the reaction conditions in the presence of both 2,2-dimethylpropyl acetate and aluminum bromide. The evidence thus seems to indicate that even neopentyl monoacetates are capable of reaction with aluminum bromide, yielding intermediates which are immediately polymerized before forming monomeric brominated products.

B) The Unassisted Displacement Reactions of Mono-and Polyacetates with Halogen-Containing Lewis Acids

The disappearance of 17% 2,2-dimethylpropyl acetate in its reaction with aluminum bromide after one hour of heating at 110° demonstrated the reactivity of monoacetate esters under these conditions. Further evidence of this type of displacement was obtained from a study of the reaction of 1,6-hexanediol diacetate with aluminum bromide. Since the interaction of these two acetoxy groups would be accompanied by an unfavorable loss of entropy any displacement products occurring in this system must have been the result of an unassisted displacement. Previous investigation of this reaction had revealed 1,6-dibromohexane as the only recovered product (equation 6,p.10). The results, as summarized in Table XVI (p.110), show 1,6-dibromohexane and 6-bromohexyl acetate to be the major products of the reaction.

The calculated extent of reaction at the higher temperature indicates as in the 1,2-ethanediol diacetate system (Table XIV,p.103), that the reaction had proceeded to the aluminum triacetate stage along with the formation of a substantial quantity of brominated products.

Table XVI: Reaction of 1,6-Hexanediol Diacetate with $AlBr_3$[a]

Molar Ratio[c]	Temp. °C	$CH_2Br-(CH_2)_4-CH_2Br$ / $AlBr_3$	$CH_2OAc-(CH_2)_4-CH_2Br$ / $AlBr_3$	Recovered Acetate	Extent of Reaction[b]
2:1	159 ± 3	0.90	0.75	6%	85%
2:1	158 ± 2	0.75	0.77	7%	76%
2:1	158 ± 2	0.81	0.81	8%	81%
2:1	108 ± 2	0.16	0.85	38%	34%

[a]Heated for one hour

[b]As defined in Table XIV (p.103)

[c]Ratio of ester to aluminum bromide

A further indication of the existence of an unassisted displacement pathway involving aluminum bromide was obtained from its reaction with n-butyl acetate (Table XVII).

Table XVII: Reaction of n-Butyl Acetate with $AlBr_3$[a]

Molar Ratio[d]	Temp. °C	Products	Yield[b]	Recovered[c] Acetate
4:1	154 ± 2	1-BuBr	29%	70%
		2-BuBr	3%	
4:1	152 ± 2	1-BuBr	26%	72%
		2-BuBr	3%	
4:1	108 ± 2	1-BuBr	23%	78%
4:1	107 ± 1	1-BuBr	24%	73%
4:1	107 ± 1	1-BuBr	23%	73%

[a]Heated for one hour

[b]Yields are based on the reaction stopping at the aluminum bromodiacetate stage

[c]Rearranged starting material was not found

[d]Ratio of ester to aluminum bromide

The recovery of substantial amounts of brominated product along with the consumption of 20-30% of the starting n-butyl acetate emphasized its high reactivity with the Lewis acid. A comparison of these results with those obtained from aluminum chloride, a weaker Lewis acid, under similar conditions revealed a direct correspondence between the strength of the Lewis acid and its reactivity toward n-butyl acetate (Table XVIII, p.113). In addition, the data in Table XVIII demonstrate the probable absence of a neighboring group effect in diacetates of chain length greater than three carbons as reflected by a sharp decline in the yields of chlorinated products obtained in their reaction with aluminum chloride. C_4 may react very slightly via AcO-7 participation, a reaction mode suggested in the work of Derbesy and Naudet (18).

The competitive reaction between 2,2-dimethylpropyl acetate and n-butyl acetate with aluminum bromide was studied in an effort to characterise the nature of the unassisted displacement reaction. As S_N2 reactions involving neopentyl systems undergo displacements on the average 10^{-5} times as fast as those of corresponding substituted n-butanes (89), the extent of S_N2 character should be reflected in the relative rate study described above. Similar rates of displacement would be indicative of an S_N1 mechanism as this type of process is less

Table XVIII: Reaction of Primary Alkyl Acetates with $AlCl_3$[a]

Acetate	Molar Ratio[b]	Temp. °C	Product	Yield[c]	Recovered Acetate[d]
1) n-BuOAc	4:1	154 ± 3	1-BuCl 2-BuCl[e]	9% 2%	85%
2) n-BuOAc	4:1	108 ± 2	1-BuCl 2-BuCl[e]	2% 0.5%	90%
3) 1,3-Propanediol diacetate[f]	2:1	106 ± 1	3-chloro-propyl acetate	56%	44%
4) 1,4-Butanediol diacetate	2:1	107 ± 2	4-chloro-butyl acetate	5%	87%
5) 1,5-Pentanediol diacetate	2:1	108 ± 2	5-chloro-pentyl acetate	5%	95%
6) 1,6-hexanediol diacetate	2:1	110 ± 1	6-chloro-hexyl acetate	5%	93%
7) 1,6-hexanediol diacetate	2:1	154 ± 4	6-chloro-hexyl acetate 1,6-dichloro-hexane	29% 4%	41%

[a]Heated for one hour

[b]Ratio of ester to aluminum chloride

[c]Yields are based on the reaction stopping at the aluminum chlorodiacetate stage

[d]Rearranged starting material was not found

[e]Previously identified (23)

[f]Reacts through an acetoxonium ion intermediate (Table VIII, p.93)

dependent on nucleophilic overlap in the transition state with steric factors becoming relatively less important, furthermore the rate-enhancement which may accompany the possible rearrangement of the α-methyl group would more than compensate for any existing rate inhibiting steric effects (91). The competitive reaction was performed at 115 $\pm$ 0.5° in the absence of solvent. The relative rate of reaction of 2,2-dimethylpropyl acetate to n-butyl acetate was 0.69 based on recovered starting material indicating the existence of minimal steric influences and suggesting an S_N1 process. In addition, the relative rates of reaction was found to be fairly insensitive to solvent effects as summarized in Table XIX reducing any possibility for the existence of a dual mechanism.

Table XIX: Competitive Reaction of 2,2-Dimethylpropyl Acetate and n-Butyl Acetate with $AlBr_3$

Molar Ratio	Time (Hrs.)	Solvent	Neopentyl Acetate / n-BuOAc
1:1	44.25	heptane	0.43
1:1	27.0	tetrachloroethane	0.46

The apparent S_N1 character of the unassisted displacements caused by the action of Lewis acids such as aluminum bromide on various primary acetates was further supported by the investigation of the reaction of aluminum dichloroacetate with racemic and optically active 2-octyl acetate. The aluminum dichloroacetate was formed *in situ* by the reaction of equimolar concentrations of aluminum chloride with 1,2-ethanediol diacetate at 110°. An equimolar concentration of 2-octyl acetate was then added and the reaction mixture heated for one hour at 111 ± 1°. Analysis of the resulting reaction mixture by gas chromatography (column A at 58°, 45 cc./min.) gave the following products: 5% *trans*-2-octene, 16% *cis*-2-octene, 1% 1-octene, 33% 2-chlorooctane, 16% 3-chlorooctane, and 6% 4-chlorooctane. Comparison of this data to that of the reaction of aluminum chloride with primary acetates (Table XVIII, p.113) indicates increased reactivity in the former case, typical of an S_N1 process. In addition, the predominance of products possibly arising through elimination and rearrangements also seems to indicate the involvement of a carbonium ion intermediate. However, the fact that the Lewis acid can react with either the ester or any of the chlorinated products does minimize the mechanistic significance of the product distribution.

The stereochemistry of the formation of 2-

chlorooctane was investigated by the reaction of aluminum dichloroacetate with (+)-S-2-octyl acetate. Vacuum distillation in a spinning band column permitted product separation and recovery of a mixture consisting of 63% 2-chlorooctane and 27% 3-chlorooctane, which had a rotation of $\alpha^{27}D$ - 6.67° (neat). The assumption is made that the 3-chlorooctane is optically inactive as it arises via a 1,2-hydride shift. On this basis, the specific rotation of the 2-chlorooctane is $[\alpha]^{27}D$ - 12.16° (neat). Hughes, Ingold, and Masterman have demonstrated that identical configurations of 2-octyl acetate and 2-chlorooctane have identical signs of rotation. They calculated the specific rotation of (+)-S-2-chlorooctane to be $[\alpha]^{20}D$ + 38.3° (neat) (42). Thus, if temperature effects are discounted, 66% of the 2-chlorooctane formed with inversion of configuration. In addition, unreacted 2-octyl acetate was recovered and found to have racemized to the extent of only 11%, thereby eliminating the possibility of extensive racemization prior to displacement.

The fact that displacement did not proceed with complete inversion of configuration is again suggestive of an S_N1 process. However, this interpretation of these data is of limited significance in view of possible post displacement racemization of the (-)-R-2-chlorooctane by the Lewis acid.

C) Isolation of Aluminum Triacetate

The stoichiometries of the reactions of 1,2-ethanediol diacetate and 1,6-hexanediol diacetate with aluminum bromide both require that aluminum triacetate be formed as a product (Tables XIV and XVI, p.103 and 110, respectively). An attempt was made to isolate this salt by heating aluminum bromide with excess 1,2-ethanediol diacetate at 155-160°. After 25 minutes of heating the formation of a precipitate was noted. The isolated solid was washed and dried. Elemental analysis gave results in good agreement with that expected for aluminum triacetate although the analysis gave evidence of contamination with a bromine-containing aluminum compound (p.72). The infrared spectrum (nujol mull) (fig. 2, p.78) was similar to the published spectrum of aluminum triacetate (34).

D) Solvent Effects on the Reaction of Halogen-Containing Lewis Acids with Polyol Esters

A study of the competitive reaction of 1,6-hexanediol diacetate with n-butyl acetate in the absence of solvent showed anomalous behavior as the molar ratio of the reactants was varied (Table XX).

Table XX: Competitive Reaction of 1,6-Hexanediol Diacetate and n-Butyl Acetate with $AlBr_3$ (115 ± 1°)

Molar Ratio	Time (Min.)	Relative Rate
$CH_2(OAc)-(CH_2)_4-CH_2(OAc)$ / n-BuOAc		$CH_2(OAc)-(CH_2)_4-CH_2(OAc)$ / n-BuOAc
1:1	30	2.0
2:1	20	1.15
4:1	20	0.53
1:4	20	2.0

Statistically the relative rate of reaction of 1,6-hexanediol diacetate to n-butyl acetate is expected to be 2:1. This expected value was found when the molar ratios of diacetate to monoacetate were 1:1 and 1:4. However, as the concentration of the diacetate increased, increasing

the polarity of the medium, the relative rate decreased. It thus seems that the rates of reaction of esters with halogen-containing Lewis acids are sensitive to the polarity of the medium. This observation was further supported by the results of the same competitive reaction carried out in heptane or tetrachloroethane (Table XXI, p.121), where the relative rate decreased more than two-fold in the more polar (higher dielectric constant) tetrachloroethane medium. Similar results were obtained from the competitive reaction of 1,4-butanediol diacetate and n-butyl acetate in heptane and tetrachloroethane (Table XXII, p.121).

It may be that these solvent effects are reflecting the greater ease of solvation of a complexed diacetate in a non-polar medium as compared to that of a monoacetate. Varying the polarity of the solvent had little or no effect on the relative rates of reaction of two mono-acetates, n-butyl acetate and 2,2-dimethylpropyl acetate (Table XIX, p.115).

Table XXI: Competitive Reaction of 1,6-Hexanediol Diacetate and 1-Butyl Acetate with $AlBr_3$ in Solvent (95 ± 1°)

Molar Ratio $\frac{CH_2(CH_2)_4CH_2}{OAc \quad OAc}$ / n-BuOAc	Solvent	Time	Relative Rate $\frac{CH_2(CH_2)_4CH_2}{OAc \quad OAc}$ / n-BuOAc
1:1	heptane	17.25	4.1
2:1	heptane	44.0	4.3
1:3.5	heptane	21.5	3.9
1:1.2	tetrachloroethane	18.0	1.4
1:1.4	tetrachloroethane	14.0	1.4

Table XXII: Competitive Reaction of 1,4-Butanediol Diacetate and n-Butyl Diacetate with $AlBr_3$ in Solvent (95 ± 1°)

Molar Ratio $\frac{CH_2(CH_2)_2CH_2}{OAc \quad OAc}$ / n-BuOAc	Solvent	Time	Relative Rate $\frac{CH_2(CH_2)_2CH_2}{OAc \quad OAc}$ / n-BuOAc
1:1	heptane	21.5	4.1
1:1	tetrachloroethane	19.5	1.5

Discussion

A) Displacement with Neighboring Group Assistance

The interaction of 1,2-and 1,3-polyol acetates with halogen-containing Lewis acids involves two competing reactions, both resulting in the displacement of a carboxylate group: (1) Neighboring group participation with the ultimate formation of an acetoxonium ion intermediate, and (2) unassisted displacement of one or both acetoxy groups by halogens. Both of these processes have been observed in this investigation. Obviously, monoacetates and those diacetates which have carbalkoxy groups for which an unfavorable entropy of activation reduces the possibility of their interaction e.g., 1,6-hexanediol diacetate, can only react via an unassisted displacement in forming mono- and dihalides. It is with 1,2- and 1,3-diol diacetates that the possibility of a dual mechanism exists. The reaction of aluminum chloride with 1,2-ethanediol diacetate-O^{18} and 1,3-propanediol diacetate-O^{18} (Tables VII and VIII, pp. 92 and 93, respectively) has confirmed the predominance of the neighboring group participation mechanism originally proposed by Wilen and Vanderhoek (97,106). The labeling study found 95.3 to 96.6% acetoxonium ion formation in the former, and a maximum of 97.3% for the latter. The interaction of zinc chloride with 1,3-propanediol diacetate (Table XIII, p.93) similarly indicated 94.1% acetoxonium

ion intervention. Further evidence of the predominance of this mechanistic pathway came from the results of the cis-and trans-1,2-cyclohexanediol diacetate-O^{18} reactions with aluminum chloride (Tables X and IX, respectively)(p.97). The trans isomer showed 81.8 to 87.2% neighboring group participation and, as expected, the cis isomer an insignificant amount (4.4%) of participation. This is quite reasonable since the configurational relationship of the two acyloxy groups in the cis isomer does not permit the concerted formation of an acetoxonium ion intermediate. The evidence also excludes formation of an appreciable amount of acetoxonium ion by a non-concerted process (indeed by any process).

An unexpected observation made in the study of the cis-and trans-diacetates was the absence of any evidence for anchimeric assistance in the case of the trans diacetate. The relative rate of reaction of the trans to cis diacetate was only 3.5 at 156°. Other systems exhibiting a similar type of neighboring group participation show much higher relative rates; e.g., the rate of acetolysis of trans-2-acetoxycyclohexyl brosylate is 650 times faster than that of the corresponding cis-isomer at 100° (111). However, there are other known instances where a reaction undergoes neighboring group participation without appreciable rate enhancement. The formolysis of

1-phenyl-2-propyl tosylate involves an aryl assisted pathway to the extent of 76%, but with an accompanying rate enhancement of only 4.5 (83). This enhancement however, has been shown to increase with the decreasing nucleophilicity of the solvent, and in trifluoroacetic acid measures 564 (66). If the extent of rate enhancement is a measure of the amount of push that a neighboring group can supply in order to assist in the removal of a leaving group, then it seems likely that there are two factors which influence this enhancement: 1) the nucleophilicity of the neighboring group, and 2) the strength of the leaving group. If the neighboring group is a weak nucleophile it may be unable to compete with other processes, such as displacement by solvent to effectively enhance the rate of reaction. Similarly a strong, i.e., excellent leaving group will be in less need of the push that a neighboring group can supply and thus show little or no rate enhancement. It may be that the latter is applicable to the trans-1,2-cyclohexanediol diacetate-aluminum chloride system. The complexing of an acetoxy group to aluminum chloride makes it an excellent leaving group, and as a result the reaction could exhibit little or no anchimeric assistance.

With the establishment of the involvement of five- and six-membered acetoxonium ions in these reactions, the relative rate of reaction of 1,2-ethanediol diacetate and 1,3-propanediol diacetate with aluminum chloride should permit a measurement of their relative stabilities. As a

result of this competitive rate study, it was determined that at 94 ± 0.5° the relative rate of formation and hence the relative stability of a five-membered relative to a six-membered acetoxonium ion was 5:1. The greater stability of the five-membered intermediate is in apparent agreement with published data for other cyclic intermediates (Table XXIII, p.126), the lower strain factor associated with a six-membered ring being outweighed in these examples by the more favorable entropy of activation associated with the formation of a five-membered ring (14). The stability of the five-membered intermediate over that of the six-membered one is again reflected in the higher extent of scrambling via internal return in the 1,2-ethanediol diacetate-$AlCl_3$ system (51.2%) as compared to the 1,3-propanediol diacetate-$AlCl_3$ system (13.4%).

Table XXIII: The Rate of Ring - Closure Reaction as a Function of Ring Size

Reaction	Relative Rate		Ref.
	n = 5	n = 6	
1) Acetolysis of $MeO(CH_2)_{n-1}OBS$	5.3	1.0	14
2) Hydrolysis of $HO(CH_2)_{n-1}Cl$	2.5	1.0	14
3) Hydrolysis of $^{-}O_2(CH_2)_{n-2}Cl$	1.1	1.0	14
4) Solvolysis of $\phi\text{-}\underset{\underset{O}{\|}}{C}\text{-}(CH_2)_{n-2}Cl$	35.7	1.0	72

B) Unassisted Displacements

A number of significant results were directly obtained to indicate that the unassisted displacement reaction involving halogen-containing Lewis acids with mono- and polyacetates are S_N1 in character: 1) a high relative rate ratio of 0.69 for the competitive reaction of 2,2-dimethylpropyl acetate to n-butyl acetate with aluminum bromide illustrates the absence of significant steric influences which are expected to accompany an S_N2 process, 2) the increased reactivity of Lewis acids towards secondary acetates as compared to primary ones, e.g., the reaction of aluminum dichloroacetate with 2-octyl acetate yields substantially more chlorinated product than the reaction of n-butyl acetate with aluminum chloride, and 3) the fact that the complete inversion of configuration, expected for an S_N2 displacement, is not observed in the formation of 2-octyl chloride from the reaction of (+)-S-2-octyl acetate with aluminum chloride.

Gerrard and Hudson (29-31,106) have suggested that the absence of rearranged displacement products resulting from the reaction of hydrogen halides with n-alkanols at temperatures up to 160° is indicative of an S_N2 process. These same reactions also exhibit high catalytic effects with no rearrangement when zinc chloride is added at relatively low concentrations. Here, the zinc chloride

probably functions by maintaining a high effective concentration of hydrogen chloride as the complex ions $ZnCl_3^-$ and $ZnCl_4^-$ (Scheme XI, p.99).

Scheme XI

$$ZnCl_3^- \cdots\cdots R \cdots\cdots \underset{H}{OH^+} \xrightarrow{S_N2} ZnCl_2 + RCl + H_2O$$

However, when the relative molar concentration of the HCl to zinc chloride drops to 5:1, rearrangement to a sec-alkyl group does begin to occur. The percentage of rearrangement varies considerably with the zinc chloride concentration and may be as high as 21% at 1:1 concentrations. It thus seems likely that with esters at high zinc chloride concentrations, the ionization of the C-O bond begins to be facilitated by coordination of the carbonyl oxygen with the Lewis acid which leads to an S_N1 process.

If these observations are applicable to esters a zinc chloride-HCl reagent should favor S_N2 displacement, while zinc chloride, alone should favor S_N1 displacement. As the sequence for S_N2 reactivity is primary > secondary > tertiary, this order being reversed for an S_N1 process, it might be expected that in the 1,2 and 1,3 normal primary diacetates the rate of an unassisted S_N2 process would be more competitive with neighboring group participation as

compared to an S_N1 process. The experimental evidence supports this hypothesis. Reactions of zinc chloride-HCl with 1,2-ethanediol diacetate-O^{18} (Table XI, p.99) and 1,3-propanediol diacetate-O^{18} (Table XII, p.100) show substantial reductions in the maximum extent of acetoxonium ion intervention when compared to the corresponding aluminum chloride, or zinc chloride reactions. 1,2-Ethanediol diacetate experienced a decline from 96.6% (Table VII, p.92) to 70.1% and the 1,3-diacetate from 97.5% (Table VIII, p.93) to 36.7% on going from aluminum chloride alone to zinc chloride-HCl. The 1,3-propanediol diacetate-zinc chloride system showed 94.1% acetoxonium intervention (Table XIII, p.101) as compared to 36.7% for the 1,3-propanediol diacetate-zinc chloride-HCl system. These data apparently reflect a dramatic increase in the ability of the unassisted displacement to compete with neighboring group participation in the presence of hydrogen chloride.

This evidence further supports previously cited data (p.127) which are in accord with the contention that the unassisted displacement reactions involving halogen-containing Lewis acids in the absence of HCl is an S_N1 process. The addition of HCl to the Lewis acid apparently converts the displacement to an S_N2 process. Further evidence of this can be found in the relative rate of reaction of 3-chloropropyl acetate to

2,2-dimethyl-3-chloropropyl acetate in the presence of $ZnCl_2$-HCl (Table I, p.14), this is found to be 27, a difference that may be attributable to the susceptibility of neopentyl-type compounds to rate retarding steric effects while undergoing S_N2 displacement. The operation of an inductive effect attributable to the β chlorine may be in part obscuring the neopentyl effect. Under similar conditions the relative rate of dodecyl acetate to 2,2-dimethyl-3-chloropropyl acetate is 135 (Table I, p.14). The observed difference in the maximum extent of acetoxonium ion intervention for the reactions of zinc chloride-HCl with 1,2-ethanediol diacetate-O^{18} (Table XI, p.99) and 1,3-propanediol diacetate-O^{18} (Table XII, p.100) (70.1% vs. 36.7%) can be attributed to the greater stability of the five-membered acetoxonium ion (p.125) and its resulting enhanced ability to compete with the unassisted S_N2 displacement.

In the absence of a protonic acid the competitiveness of the unassisted displacement (S_N1 in character) with neighboring group participation should increase in going from a primary to a secondary system. This fact is confirmed when the observation is made that the maximum intervention of a five-membered acetoxonium ion declines from 97.1% for 1,2-ethanediol diacetate (Table VII, p.92) to 87.2% for the <u>trans</u>-1,2-cyclohexanediol diacetate

Table IX, p.97), in the presence of aluminum chloride. The extent of internal return in both of these systems is approximately the same, 27.6 and 28.6%, respectively. This apparently reflects the similar life times and stabilities of the two five-membered acetoxonium ions. Those systems having little or no acetoxonium ion intervention such as the cis-1,2-cyclohexanediol diacetate-aluminum chloride reaction show only an insignificant degree of internal return.

The S_N1 characteristics of the unassisted displacement reactions of acetates with halogen-containing Lewis acids suggest that the rates of these reactions should be directly proportional to the ease of cleavage of the C-O bond. Coordination of an acetoxy group at the carbonyl oxygen with a Lewis acid will weaken the C-O bond and may, as with the Lewis acids studied, lead to its cleavage. The rate of bond breaking will be directly proportional to the strength of the coordinate bond and the Lewis acid, e.g., $AlBr_3 > AlCl_3 > ZnCl_2$. This order is reflected in the greater reactivity of aluminum bromide towards n-butyl acetate (Table XVII, p.111) as compared to that of aluminum chloride (Table XVIII, p.113).

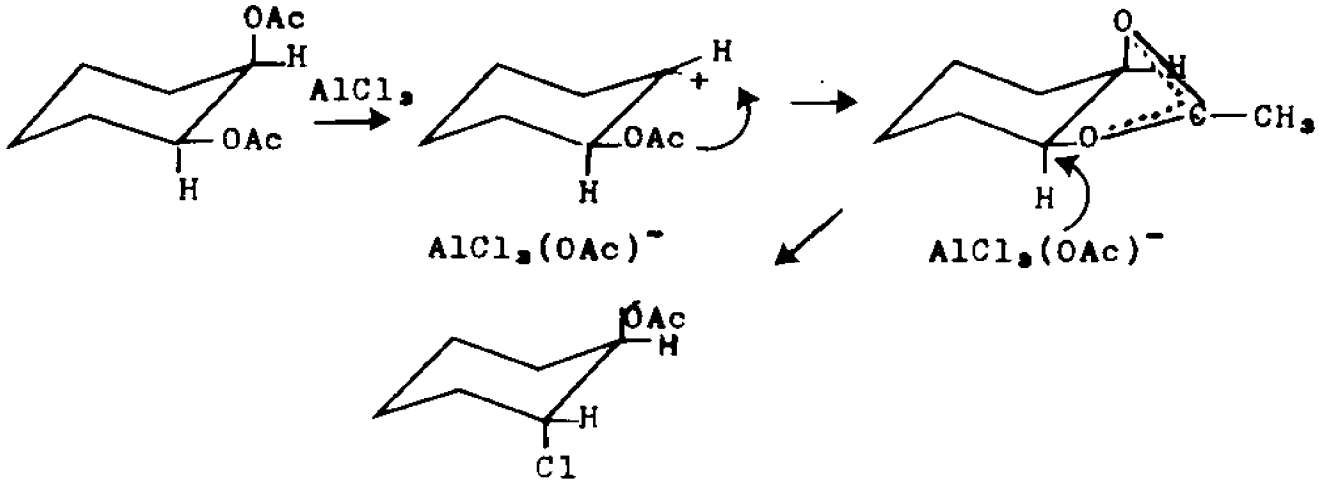
Concurrently the greater strength of aluminum bromodiacetate as a Lewis acid over that of aluminum chlorodiacetate is a significant factor in accounting for its reactivity with diol acetates in either an assisted (Table XIV, p.103) or unassisted displacement (Table XVI,

p.110). The aluminum chlorodiacetate salt has as yet not been found to be reactive towards diol diacetates.

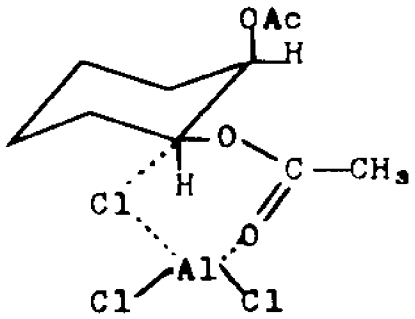
While the stereochemistry of the unassisted displacement reactions of halogen-containing Lewis acids with acyclic secondary acetates, e.g., (+)-S-2-octyl acetate and aluminum dichloroacetate, indicates a displacement proceeding with predominant, not exclusive, inversion of configuration, the cyclic trans-and cis-1,2-cyclohexane-diol diacetates show no such behavior. Both of these diacetates in their reaction with aluminum chloride yield the trans-2-chlorocyclohexyl acetate with no detectable cis isomer. The former proceeds with 12.8-18.2% and latter with 96% unassisted displacement, as shown by O^{18} labeling studies (Tables IX and X, p.97). This suggests that the unassisted displacement on the trans diacetate proceeded exclusively with retention of configuration and on the cis diacetate with complete inversion of configuration.

The O-18 labeling experiments did eliminate the possible existence of a stepwise formation of an acetoxonium ion in the cis diacetate isomer (Scheme XII) (p.133).

Scheme XII



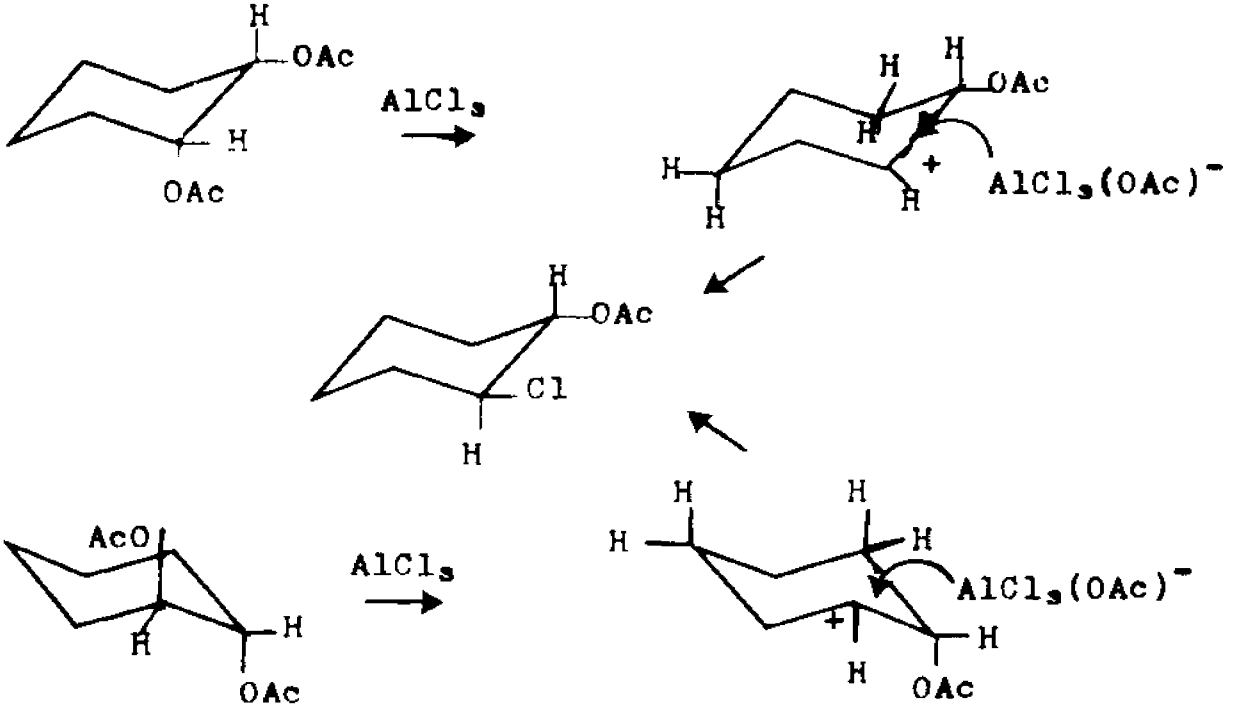
The cyclic intermediate formed in S_Ni reaction, was considered as a possible participant in displacement with exclusive inversion of configuration in the cis diacetate isomer. Construction of a Prentice-Hall model showed the proposed intermediate (XVI) to be an excessively strained one. This and the lack of precedence for such a reaction made this possibility rather unlikely.



XVI

The stereoselectivity of these displacements could be accounted for by attack on the least hindered side of the cyclohexane ring by the incoming nucleophilic anion, $AlCl_3(OAc)^-$, as outlined in Scheme XIII.

Scheme XIII



In cis-1,2-cyclohexanediol diacetate the approach of the bulky $AlCl_3(OAc)^-$ ion is strongly inhibited by the axial hydrogens in the 3 and 5 positions forcing the nucleophile to attack from the opposite side to form the trans product. In the trans-1,2-cyclohexanediol diacetate case the axial 2-acetoxy group sterically hinders the approach of the $AlCl_3(OAc)^-$ directing the attack to the unhindered side to yield a trans product.

C) Synthesis of cis-1,2-Cyclohexanediol

During the course of this study it became necessary to synthesize cis-1,2-cyclohexanediol on a relatively large scale. Three known approaches involving the stereospecific oxidation of cyclohexene to the cis-1,2-diol were considered: 1) Oxidation with osmium tetroxide (35), 2) the Woodward modification of the Prevost reaction (12), and 3) potassium permanganate oxidation (104). The first two were both considered to be expensive and uneconomical, while the latter had been shown to be both time consuming and resulting in inferior yields.

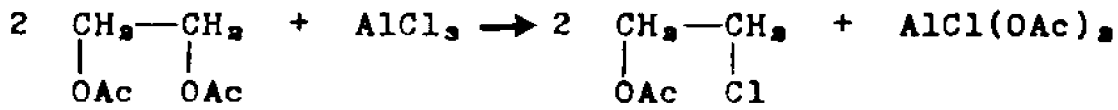
Ultimately it was decided to attempt a stereospecific reduction of catechol by hydrogenation at high pressures (115). Hydrogenation at 2000 p.s.i. at 125° in the presence of 5% ruthenium on carbon (see p.35) gave a crude solid product which nmr analysis revealed to be a mixture of two 1,2-cyclohexanediol isomers. The cis:trans ratio was found to be 60:40 by peak area integration of the nmr spectrum. However, three recrystallizations in carbon tetrachloride yielded cis-1,2-cyclohexanediol in purity greater than 99%. The latter was confirmed by conversion to the corresponding diacetate and g.c. analysis (column B at 190°, 60 cc./min.) (see p.36). The maximum yield obtained is 24%.

Though the yield for the procedure may presently be considered low, the method does present a rapid and

inexpensive approach to the large scale synthesis of cis-1,2-cyclohexanediol. Future studies will be aimed at increasing the cis:trans product ratio resulting from the hydrogenation.

Abstract

Reactions such as



which occur at about 150° lead to displacement of some but not all of the acetoxy groups by chlorine. Thus, 2-chloroethyl acetate is virtually inert to aluminum chloride under the reaction conditions used.

An oxygen-18 label study was employed as a means of establishing the intervention of an acetoxonium ion intermediate in the displacement reactions of 1,2-and 1,3-polyol diacetates with aluminum chloride, zinc chloride, and zinc chloride-HCl. The intervention of this intermediate was further confirmed by examining the reaction of aluminum chloride with cis-and trans-1,2-cyclohexanediol diacetate-O^{18}. The greater stability of a five-membered acetoxonium ion relative to that of a six-membered one by a factor of five at 94 ± 0.5° was established from the results of the competitive reaction of aluminum chloride with 1,2-ethanediol diacetate and 1,3-propanediol diacetate.

The apparent absence of steric effects in the displacement reaction of neopentyl-type acetates with aluminum bromide, the increased reactivity of aluminum chloride towards secondary acetates as compared to primary

ones, the absence of complete inversion of configuration in the formation of 2-octyl chloride from (+)-S-2-octyl acetate with aluminum chloride, and the inability of an unassisted displacement reaction to compete effectively with an assisted displacement in the presence of zinc chloride and diprimary diacetates led to the conclusion that the unassisted displacement reaction of halogen-containing Lewis acids with carboxylates are S_N1 in character. The addition of HCl to zinc chloride significantly shifts the character of the displacement to S_N2.

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