National Library
of Canada

Canadian Theses Service

Ottawa, Canada
K1A 0N4

Bibliothèque nationale
du Canada

Services des thèses canadiennes

CANADIAN THESES

THÈSES CANADIENNES

NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30. Please read the authorization forms which accompany this thesis.

AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30. Veuillez prendre connaissance des formules d'autorisation qui accompagnent cette thèse.

THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED

LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE

Canada

NL 339 (r 86/01)

National Library of Canada
Ottawa, Canada
K1A 0N4

Bibliothèque nationale du Canada

TC

ISI 0-315-23273-0

CANADIAN THESES ON MICROFICHE SERVICE – SERVICE DES THÈSES CANADIENNES SUR MICROFICHE

PERMISION TO MICROFILM – AUTORISATION DE MICROFILMER

lease print or type – Écrire en lettres moulées ou dactylographier

AUTHOR – AUTEUR

Name of Author – Nom complet de l'auteur

WONG, KENNETH CHUNG-ON

e of Birth – Date de naissance

JULY 24 /1954

Canadian Citizen – Citoyen canadien

☐ Yes / Oui ☒ No / Non

ıntry of Birth – Lieu de naissance

HONG KONG

Permanent Address – Résidence fixe

10 JORDAN RD
12/F GLORY COURT KOWLOON HONG KONG

THESIS – THÈSE

e of Thesis – Titre de la thèse

ON THE MECHANISM OF METAL HYDRIDE REDUCTIONS OF 9-FLUORENONES

gree for which thesis was presented
ade pour lequel cette thèse fut présentée

M. Sc

Year this degree conferred
Année d'obtention de ce grade

1985

iversity – Université

UNIVERSITY OF ALBERTA

Name of Supervisor – Nom du directeur de thèse

DENNIS D TANNER

AUTHORIZATION – AUTORISATION

rmission is hereby granted to the NATIONAL LIBRARY OF CANADA to **crofilm** this thesis and to **lend** or **sell copies of the film.**

e author reserves other publication rights, and neither the thesis nor extene extracts from it may be printed or otherwise reproduced without the :hor's written permission.

L'autorisation est, par la présente, accordée à la BIBLIOTHÈQUE NATIONALE DU CANADA de **microfilmer** cette thèse et de **prêter** ou de **vendre des exemplaires du film.**

L'auteur se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans l'autorisation écrite de l'auteur.

ATTACH FORM TO THESIS – VEUILLEZ JOINDRE CE FORMULAIRE À LA THÈSE

ınature

Kenneth C. Wong

Date

August 21/1985

91 (r. 84/03)

Canada

THE UNIVERSITY OF ALBERTA

ON THE MECHANISM OF METAL HYDRIDE REDUCTION OF α-FLUOROKETONES

BY

KENNETH C.O. WONG

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE
OF
MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
FALL, 1985

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR: KENNETH C.O. WONG

TITLE OF THESIS: ON THE MECHANISM OF METAL HYDRIDE REDUCTION OF α-FLUOROKETONES

DEGREE FOR WHICH THESIS WAS PRESENTED: M.Sc.

YEAR THIS DEGREE GRANTED: 1985

(Signed) ....

PERMANENT ADDRESS:

10 Jordan Road
Kowloon, Hong Kong

DATED ..[illegible]..............1985

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

ON THE MECHANISM OF METAL HYDRIDE REDUCTION
OF α-FLUOROKETONES

submitted by KENNETH C.Q. WONG in partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

Dennis D. Tanner
Supervisor

John Hooz

Josef Takats

External Examiner

Date August 21/1985

ABSTRACT

The reductions of α-fluoroacetophenone and cyclohexyl fluoromethyl ketone with lithium aluminum hydride and aluminum hydride were carried out. Dehalogenation of these substrates occurs with either hydride reagent and is associated with the corresponding fluorohydrins. The aromatic substrate reacts with LAH to give a mixture of 1-phenyl- and 2-phenylethanols, the latter being in significant yield in benzene and only in traces in tetrahydrofuran. Defluorination is suppressed in the presence of radical inhibitors, particularly for the reaction in benzene. An electron transfer mechanism, which consists of a radical chain propagation, is proposed for the LAH defluorination of the fluorohydrin, 2-fluoro-1-phenylethanol. The LAH reduction of the aliphatic substrate furnishes a small amount of 1-cyclohexyl-1,2-epoxyethane in addition to 1-cyclohexylethanol. With a sufficient amount of hydride, the latter is the major product and arises primarily from the epoxide.

An electron transfer process could not be demonstrated for the reaction of α-fluoroacetophenone with aluminum hydride in THF, since the process is not affected by a radical inhibitor. Yet the products are similar to those from the LAH reaction. 1-Phenylethanol predominates in the product mixture obtained from the reduction with

excess hydride reagent while 2-phenylethanol prevails when a limited amount of aluminum hydride is used. On the basis of the results from the reduction with aluminum deuteride and of the product ratios of the isomeric defluorinated alcohols at various levels of the hydride reagent, it is concluded that phenyl migration of the fluoroalkoxide followed by reduction leads to the primary alcohol whereas the secondary alcohol arises from intermolecular hydride transfer of the fluoroalkoxide. The result for the reduction of cyclohexyl fluoromethyl ketone resembles that for the LAH reaction, except that the epoxide is produced in higher yield and that cyclohexyl methyl ketone is a product when a limited amount of the hydride reagent is employed. The latter finding is consistent with a hydride shift mechanism. However, this pathway accounts for only a small fraction of the product 1-cyclohexylethanol since deuteration at C-1 of this product is insignificant with aluminum deuteride. The major route from which this alcohol is derived probably involves an epoxide intermediate. An alkyl shift is also observed, though it is even less important than the migration of hydrogen.

ACKNOWLEDGEMENTS

I would like to thank Professor Dennis Tanner for his supervision of the project and his continuous support throughout the preparation of this dissertation. My gratitude is due to the colleagues in the group for their valuable discussion and assistance, in particular, to Dr. Iwao Urasaki who carried out the preliminary experiments on LAH, to Ms. Patricia Lane who carried out the preliminary experiments on aluminum hydride and also to Charles Lai and Chris Meintzer whose advice at the onset of this work has proved to be crucial. I am indebted to the staff of the Analytical Services Laboratories of the Department, especially to Messrs. Glen Bigam, Tom Brisbane (both of the high field nmr laboratory), John Olekszyk (mass spectrometry lab) and Jim Hoyle (spectral services lab). Finally I deeply appreciate the kindness of Ms. Dowhaniuk who typed this script.

TABLE OF CONTENTS

Page

SECTION

I. INTRODUCTION

II. RESULTS

Table of Contents (continued):

Page

LIST OF TABLES

Page

List of Tables (continued):

Page

LIST OF FIGURES

INTRODUCTION

I.1 Background

Ever since the initial report of its discovery and application to the reduction of common organic compounds,[1] lithium aluminum hydride (LAH) has widely been employed as a useful reducing agent. In contrast to the great versatility of LAH, aluminum hydride is a milder and hence more selective reagent. It was first prepared from aluminum chloride by Schlesinger and coworkers[1a] during their preliminary studies on the behaviour of LAH towards common inorganic reagents.

$$3\,LiAlH_4 + AlCl_3 \xrightarrow{Et_2O} 3\,LiCl_{(s)} + 4\,AlH_3 \qquad (1)$$

An exceedingly convenient method to prepare a THF solution of aluminum hydride involves the treatment of a solution of LAH with 100% sulfuric acid:[2]

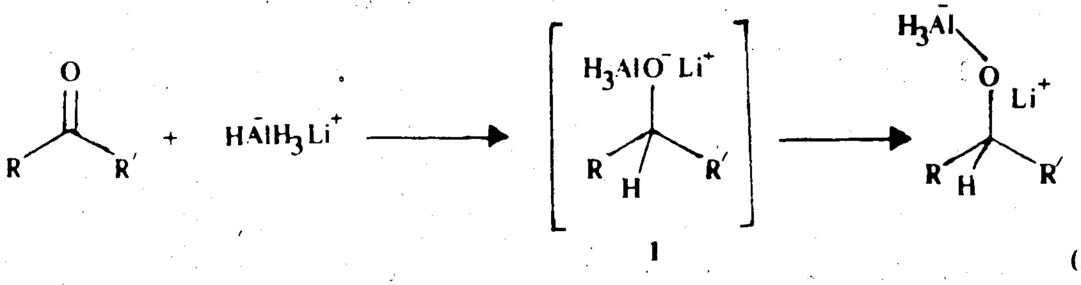
$$2\,LiAlH_4 + H_2SO_4 \xrightarrow{THF} Li_2SO_{4\,(s)} + 2\,AlH_3 + H_{2(g)} \qquad (2)$$

Studies of the physical and spectroscopic properties of LAH and aluminum hydride in solutions are helpful in the understanding of certain mechanistic aspects of their reactions with various organic functional groups. Specific conductivity measurements of diethyl ether[3] and THF solutions of LAH[3b,4] suggested the presence of ionic species. Ashby and coworkers[4a] have further demonstrated the presence of free ions and ion pairs in dilute THF solutions and triple ions at higher concentrations (>0.1 M). They have also presented thermodynamical data showing the dominancy of solvent separated ion pairs in solutions of LAH. This was substantiated by the infrared absorption bands attributed to the vibration of Li^+ within the THF solvent cage. On the other hand, both Raman and infrared data of aluminohydride ion (AlH_4^-) in ether solutions (diethyl ether, THF, dimethyl ether and 1,2-dimethoxyethane) produced by Shirk and Shriver[5] have precluded solvent coordination to the anion with strong evidence, despite contradictory proposals by earlier workers.[6] It still remains indisputable, however, that AlH_4^- is tetrahedral since the pioneer studies of the vibrational spectra of LAH solutions by Lippincott.[7]

Aluminum hydride prepared from LAH-$AlCl_3$ mixture (Equation 1) in diethyl ether polymerizes rapidly to an ether-insoluble product,[1a,8] an additional equivalence of $AlCl_3$ can prevent or reverse polymerization by forming the soluble $AlH_3 \cdot AlCl_3$. In a stronger base THF it is more stable and forms the monoetherate AlH_3.THF above −5° and dietherate AlH_3.2 THF between -45° and -5°. While ether linkage is resistant to LAH even at 80°-100°,[10,11] the cleavage of THF to 1-butanol by AlH_3, prepared from $AlCl_3$, has been reported.[12] AlH_3 obtained by Brown's procedure (Equation 2)[2] is more stable; at room temperature a solution of 0.50 M decreases to 0.49 M after 3 days.[13]

Although LAH has long been known to reduce a variety of functional types[14] except possibly the ether linkage[15] and isolated carbon-carbon multiple bonds,[16] the mechanisms of its reactions are still controversial. It appears that the substrate plays a crucial role. Trevoy and Brown,[17] in the earliest statements on the mechanisms of LAH reactions, postulated the displacement of an electronegative atom (oxygen, nitrogen or halogen) attached to carbon by hydrogen from $AlX_nH_{4-n}^-$ (n = 0-4). Since then an S_N2 mechanism has been invoked in many cases to explain LAH reduction. On the other hand, there has been a growing number of reports in the past decade highlighting the role of LAH as a single electron donor with some organic substrates. As early as 1964, Lemaine and coworkers[18] had recorded the electron spin resonance (ESR) spectrum of a paramagnetic species generated when a benzene solution of nitrobenzene was mixed with 0.25 molar equivalence LAH. This species was identified to be diphenylnitroxide radical. When the mixture was diluted with diethylene glycol, another radical species, phenylnitroxide, was produced. Likewise, the ESR spectra of radical species from nitrosobenzene and nitro-tert-butane were detected in the presence of deficient amounts of LAH.

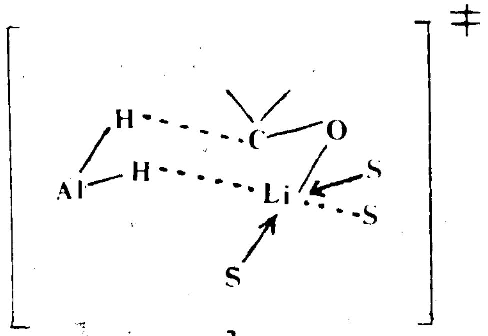
The reduction of carbonyl compounds with LAH have generally been envisioned as the transfer of a hydride anion from aluminohydride to the carbonyl carbon atom followed by the association of the oxygen atom with aluminum hydride to give an alkoxide (3).[19,20] The



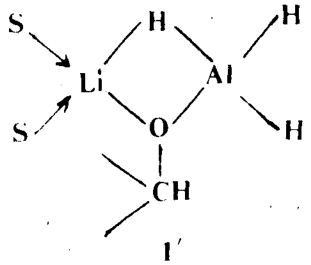
(3)

lithium cation, presumably, assists the displacement of a carbon-oxygen bond.

Ashby and Boone[21] have studied the kinetics of the reductions of mesitylphenyl ketone with LAH and sodium borohydride (NBH) in THF and concluded that either reaction is overall second order - first order in the hydride and first order in the ketone. The formation of 1 is then rate-determining. A six-membered transition state, 2, in which Li^+ is closely associated with the carbonyl oxygen, was recommended for this step based on the estimation of a lower entropy of activation than that



2



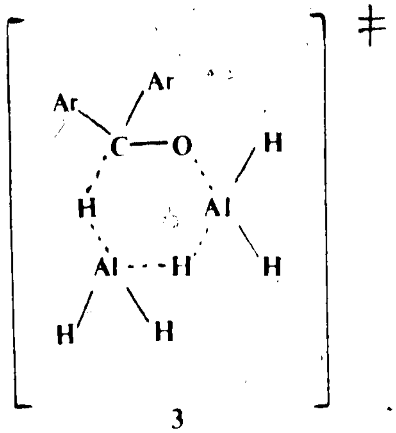
1'

(S = Solvent)

of the NBH reaction and on the knowledge[4a] that Li^+ and AlH_4^- are solvent separated in THF. The actual structure of 1 was depicted as 1'. Their results for aromatic ketones have been confirmed.[22]

If bimolecular displacement occurs as portrayed, it would be expected that the transfer of hydride proceeds from the less hindered side of the carbonyl carbon. The hydroxyl group of the alcohol product from a cyclic ketone would be cis to the hindered group. This was observed in the reduction of d-camphor where isoborneol, the cis form, was produced in not less than 90%.[23] However the more stable trans isomer prevails in the relatively less hindered 2-methylcyclohexanone.[24] This led to the early belief[25] that the transition state for the reduction of unhindered ketones was product-like and of the hindered ones, reactant-like. Subsequent investigations[26] indicated that in all metal hydride reductions of carbonyls, stereochemical course was dictated by an interplay of steric interference, torsional strain and electrostatic effects in the transition state which resembled the reactant. More recently the old idea received reassessment[27] during the course of comparative studies of the reactions of cyclic ketones with LAH and with methyllithium. Yet the low Hammett ρ values for the LAH reduction of aromatic ketones[22] and a normal kinetic isotope effect ($k_{LAH}/k_{LAD} > 1$)[21,22] for the reaction are diagnostic of an early transition state.

The mechanism of the reduction of carbonyl compounds to alcohols by aluminum hydride resembles that by LAH. On the basis of their studies of a series of cyclic and bicyclic ketones, several groups of workers have concluded that steric requirements in the reactants determine the stereochemical outcome of the reaction.[25b,28] Ayres and coworkers[28c] have reported a small positive slope from the Hammett plot for the AlH_3 reduction of <u>para-para</u> disubstituted benzophenones. They also found that only a small proportion of the hydrogen atoms of AlH_3 were available for the actual reduction. This was consistent with the cyclic transition state 3 assumed for aluminum



3

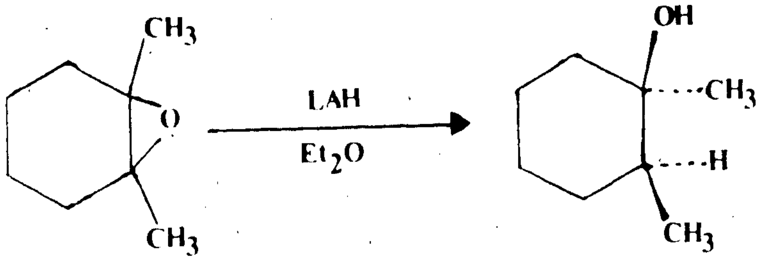
hydride reduction. Furthermore, they observed that a mixture of AlH_3 and 5 equivalents of tri-*tert*-butoxylaluminum reduced benzophenone and its halogen derivatives to a limited extent, but dimethyl- and dimethoxybenzophenones did not react. This was attributed to the formation of dialkoxyaluminum hydride (**4**) from AlH_3 and $Al(OR)_3$ as shown in Equation 4:

$$AlH_3 + 2\,(RO)_3Al \rightleftharpoons 3\,\underset{\mathbf{4}}{Al(OR)_2H} \qquad (4)$$

Compound **4** is inert towards aromatic ketones.

The bulk of evidences which supports bimolecular nucleophilic substitution has been provided by the studies of the LAH reaction of epoxides and organic halides. The corresponding studies with AlH_3 have also been carried out.

The opening of 1,2-dimethyl-1,2-epoxycyclohexane by LAH has been shown[17,29] to give 1,2-dimethylcyclohexanol (5) as depicted in Equation 5:



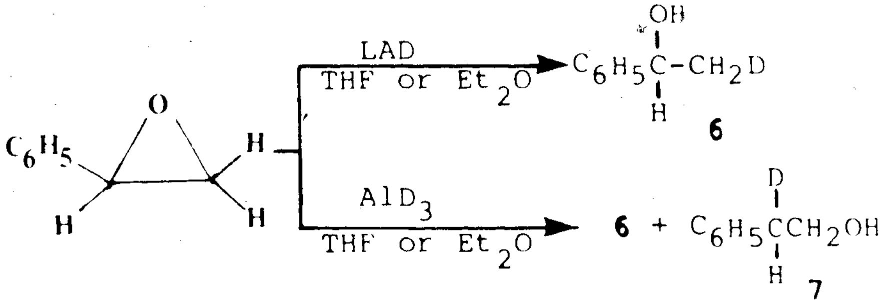
5

(5)

Yet Rickborn and coworkers have pointed out that the opening of cyclohexene oxides is more complicated than a simple S_N2 displacement, for instance, cyclohexanones have been shown to be intermediates in some cases.[29-31] The regio- and the stereochemistry of ring openings of simple unsymmetrical epoxides by LAH and aluminum hydride have offered important documentations for bimolecular displacement. In neutral or basic medium, epoxides undergo nucleophilic attack more readily at the less highly substituted carbon whereas protonation of oxygen in acidic medium or coordination with a Lewis acid facilitates ring opening to yield the more highly substituted carbocation prior to nucleophilic attack.[32,33] Thus the preponderance of the more highly substituted alcohol derived from the attack of LAH at the less hindered carbon is an indication of an S_N2

pathway.[2,13,17,29,30,34] Fuchs and Vander Werf[34] found that the percent of alcohol arising from the attack at the secondary carbon atom of 3,4-epoxy-1-butene increased with the ratio of LAH to the substrate. Partial alcoholysis of the hydride preceding the reduction depressed the percent of secondary attack. This directly supported the postulate[17] that a series of aluminohydride, $AlX_nH^-_{4-n}$ (n = 0-4) was involved in LAH reaction of organic substrates. The importance of steric effects has been enforced by the fact that tri- and tetrasubstituted expoxides exhibit low reactivity towards LAH whilst the mono- and disubstituted ones usually furnish good yields;[35]

As expected, aluminum hydride enhances attack at the more hindered carbon due to its Lewis acid character. The equations in Scheme I summarize the reactions of styrene oxide with lithium aluminum deuteride (LAD), and AlD_3.



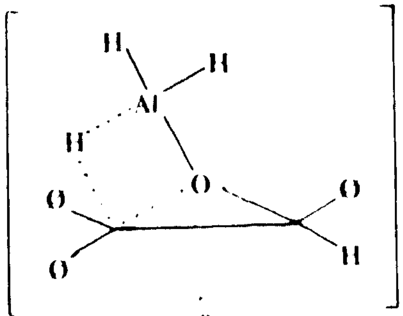
(6)

(7)

Scheme I

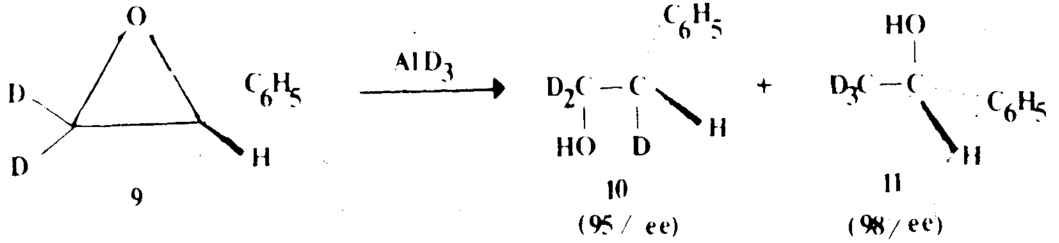
The openings of styrene oxides by LAH and AlH_3 have been the subject of active discussions.[13,35-42] With LAH, the attack at the less hindered carbon of unsubstituted styrene oxide is not exclusive since 5-10% of 2-phenylethanol is usually produced along with the major product, 1-phenylethanol.[13,17,41,43] With AlD_3, regardless of the method of preparation,[1a,2] **6** and 7 are obtained in comparable quantities.[36] In general, 1-phenylethanol still prevails from the AlH_3 reaction but not as much as in the corresponding LAH reduction.[2,13,39,41]

Eliel and coworkers[39] first observed the incorporation of deuterium at the β-carbon of the less substituted alcohol formed from styrene oxide or triphenylethylene oxide with AlD_3. The results have been confirmed in other systems.[43,44] It is widely believed that the formation of the less substituted alcohol involves initial complexation of the epoxy oxygen with AlH_3, followed by nucleophilic attack at the more highly substituted carbon. Ashby and coworkers[37,41] prompted an intramolecular hydride transfer mechanism via a 4-centered transition state **8** for the ring rupture of triphenylethylene oxide.



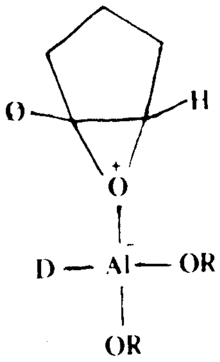
8

This mechanism predicts that a chiral center reacts with retention of configuration. Experimentally, contradictory results were found. Mosher and coworkers[36] demonstrated that the reaction of (R)-(+)-styrene-2,2-d_2 oxide (**9**) with aluminum deuteride in diethyl ether or THF is highly stereospecific. From Equation 8, the primary alcohol **10** is an inversion product, and its formation contradicted the results predicted for a 4-centered mechanism. Similarly, no evidence for cis opening have been reported for 1-substituted-1,2-epoxycyclohexanes. In 1-phenyl-1,2-epoxycyclopentane, both cis and trans 2-phenylcyclo-

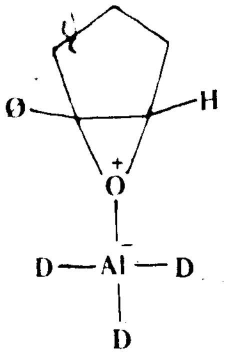


(8)

pentanol-1-d (69% and 18% respectively) are obtained with insufficient amount of AlD_3.[43] Sufficient amount of the deuteride still produces *cis* 2-phenylcyclopentanol-2-d predominantly. According to Lansbury and coworkers,[43b] intermolecular *trans* attack occurred if enough AlD_3 was present, while a deficiency in AlD_3 gave rise to intermediate species such as **12a** which opened up at the carbon-oxygen bond more readily than species of weaker Lewis acid character such as **12b**. 1,2-Hydride shift followed and ultimately furnished a mixture of 1-deuterated alcohols. The stronger Lewis acid character of **12a** was contested by Ashby *et al*[45] who claimed that the Lewis acidities of AlH_3, $AlH_2(OR)$ and $AlH(OR)_2$ were comparable since similar product compositions were obtained when the reactions of styrene oxides were effected by AlH_3 and its alkoxy-substituted counterparts respectively.



12a



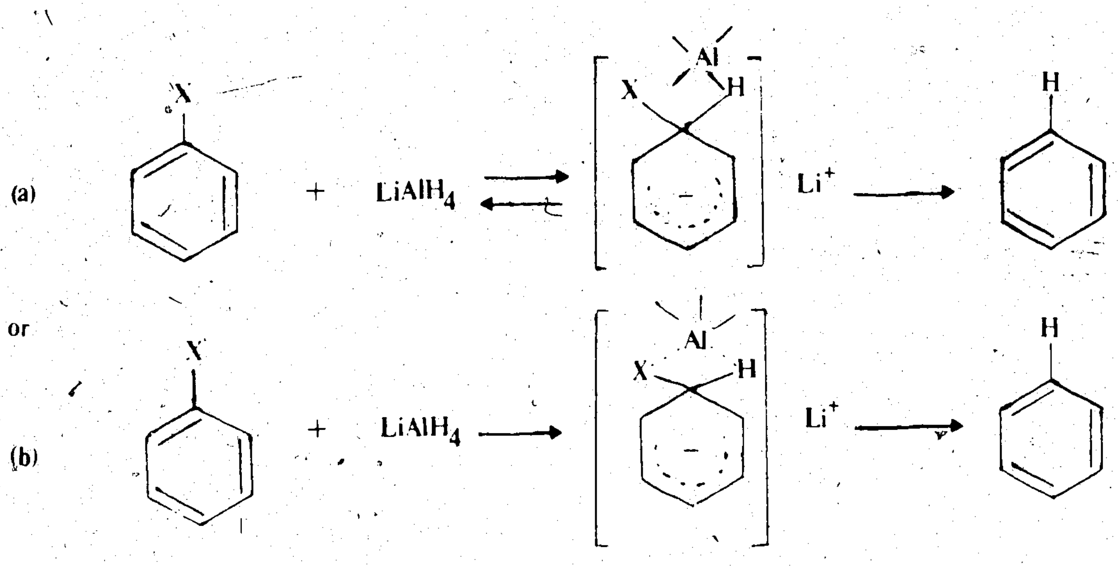
12b

The hydrogenolysis of organic halides by LAH represents a general method for the generation of hydrocarbons. Walden inversion was first demonstrated by Eliel[46] in the reduction of optically active α-chloroethylbenzene with LAD, though maximum optical rotation was not observed. Subsequent workers have similarly established net inversion in configuration for chlorides, bromides and *p*-toluenesulfonates.[47-49] Reactivity studies of alkyl halides have revealed two other important aspects characteristic of bimolecular nucleophilic displacement, viz : the orders of reactivity of aliphatic R-X are X : I > Br > Cl for the same R and R : primary > secondary > tertiary, for a given halogen.[2,17,50,51] In addition, Brown and Krishnamurthy[2] noted the following trends : benzylic ≈ allylic > primary; isobutyl >> neopentyl; cyclopentyl > 2-octyl > cycloheptyl > cyclooctyl > cyclohexyl. Earlier, Malter and coworkers[52] had demonstrated second order kinetics for the reduction of primary bromides - first order in LAH and first order in halide.

The carbon-halogen bond is relatively resistant to hydrogenolysis by aluminum hydride. Krishnamurthy and Brown[51] found that bromides reacted faster than chlorides and that the following trend of increasing reactivity, reminiscent of those with LAH, held : benzylic > primary >

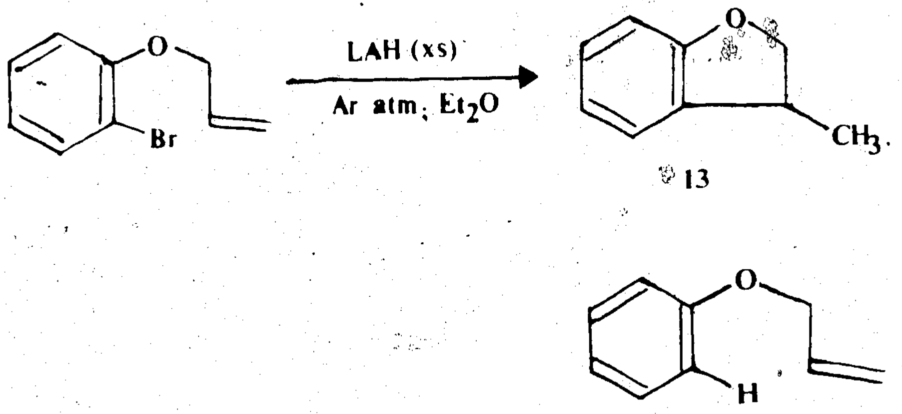
secondary ≈ cyclopentyl > cyclohexyl. Since the reaction usually proceeds much more slowly than the corresponding LAH reduction, advantage has been taken of this low reactivity in the selective reduction of other functional groups in compounds where retention of halogen is desired. Thus, 3-chloropropionic acid is converted mainly to 3-chloropropanol with aluminum hydride while the corresponding reaction with LAH yields chiefly 1-propanol.[53]

The reduction of aromatic halides was reported[17,50,54] to be slow with lithium aluminum hydride especially for the chlorides, but α,α,α,2-tetrafluorotoluene had been shown[55] to be converted to α,α,α-trifluorotoluene. Brown and Krishnamurthy[56] contended that the use of slurries of LAH in reactions by earlier workers partly accounted for the low reactivity. In their hands, all monohalobenzenes have been found to be reactive in THF. The rates of reaction are in the decreasing order of I > Br > Cl > F, which is exactly the reverse order predicted for aromatic nucleophilic substitution.[57] This trend of reactivity has also been observed by other workers.[54] The S_NAr mechanism comprises a rate-determining step of ipso attack of the nucleophile without the potential leaving group being displaced. Hence electron-withdrawing leaving groups and/or para-substituents enhance the process while electron-donating leaving groups and/or _para_-substituents suppress it. The fact that electron-withdrawing and electron-donating _para_-groups increase and decrease the rate of the reaction between aryl halides and LAH respectively presented a dilemma to these workers. Nevertheless, they observed that _o_-bromo-_tert_-butylbenzene was dehalogenated much faster than its _para_ analog, suggesting the significance of the release of steric strain as the halogen moves out of the plane to form the sp^3 carbon in the rate-determining step. Two possible mechanisms were proposed to account for the observed polar and steric effects:



Scheme II

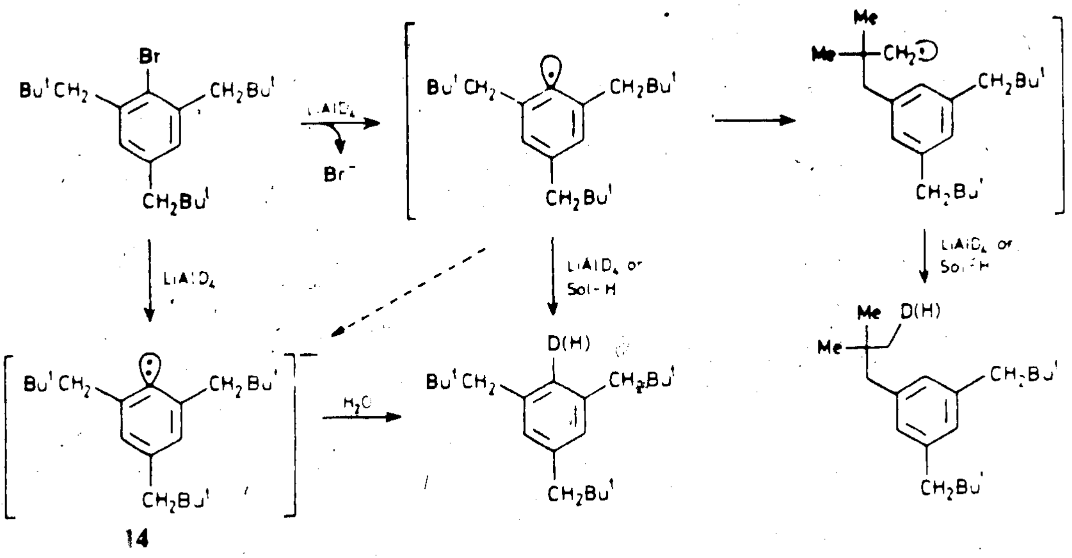
Perhaps neither mechanism in Scheme II can explain the results for reactants with cyclizable substituents on the aromatic rings. In 1979, Chung and Chung[58] suggested the intermediacy of aryl radical to account for the high yield of cyclizable product (**13**) in the reduction of vinyl-o-bromophenyl ether.



(9)

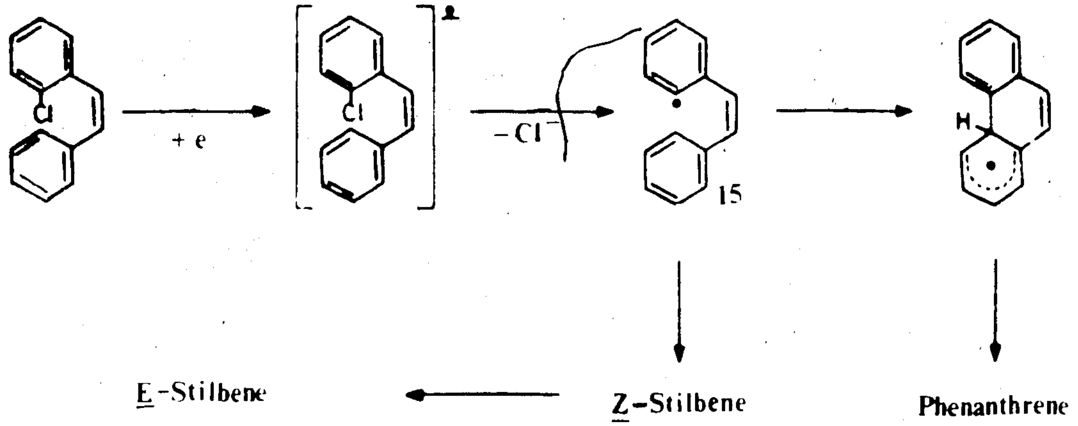
Prior to this, Barltrop and Bradbury[59] had presented evidence for the intermediacy of radicals during the course of the photoreduction of halobenzenes with sodium borohydride. In the current case, hydrogen atom abstraction was demonstrated when the reaction with LAD gave 50% deuterium-free species in the cyclization products. Less cyclization was detected in THF, which is a better hydrogen atom donor than diethyl ether. However, when Ashby and coworkers[60] attempted the reaction they obtained only a 3% total yield after 7 days. Karabatsos and Stone[54] had noted that o-bromoanisole reacted faster than its para counterpart to yield a mixture of anisole, phenol and bromophenol. Furthermore, o-methoxybenzyl alcohol was found to be converted to o-hydroxylbenzyl alcohol faster than o-methylanisole to o-methylphenol. This led to the suggestion of an intramolecular hydride transfer mechanism.

Recently, Chung and Filmore[61] extended the radical-intermediacy proposal to the reduction of 2,4,6-trineopentylbromobenzene. They observed that a substantial amount of deuterium was incorporated in the neopentyl side chain during the course of the reaction with LAD. Moreover, 28% deuterated product, largely incorporated on the ring, was generated from the LAH reaction followed by work-up with D_2O. On the basis of these results, they suggested that a carbanion intermediate (**14**), which arose from the radical precursor or from the starting substrate directly, was one possible candidate to give the undeuterated parent hydrocarbon.



Scheme III

This is depicted in Scheme III. Singh and coworkers[62] prompted an electron transfer mechanism for the reduction of Z-2-chlorostilbene on the ground of cyclization accompanying the reaction. The presence of a radical trap, cumene or cyclohexene, suppressed cyclization. Z- and E-Stilbenes were also produced. AlH_4^- was considered as the prime electron donor to the reactant, forming an aryl radical (**15**) upon the expulsion of Cl^-. The aryl radical preferentially undergoes intramolecular phenylation rather than hydrogen abstraction unless a good hydrogen atom donor like cumene or cyclohexene is available. AlH_4^- was also regarded as a hydrogen atom donor for the aryl radical to give Z-stilbene, which may isomerize to the more stable E-stilbene in the presence of excess LAH, again via a radical process. Scheme IV outlines their proposed mechanism.



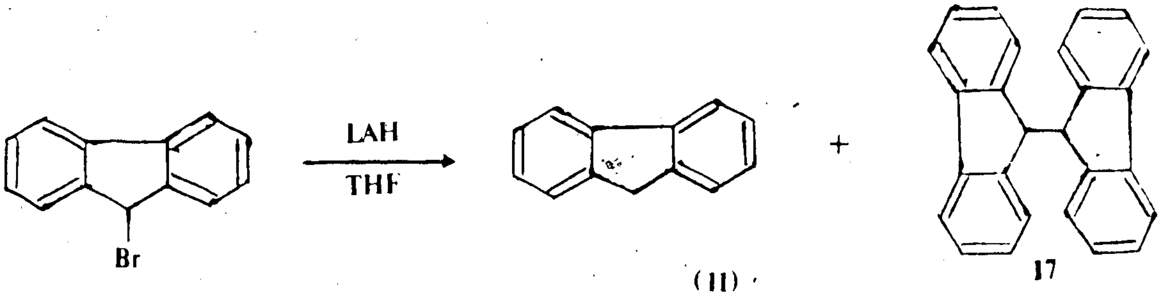
Scheme IV

Chung[63] noted that the reduction of aryl halides with LAH was not inhibited by tetraphenylhydrazine or 9,10-dihydroanthracene, hence excluding a chain process.

Benzyl halides are susceptible to hydrogenolysis by LAH. Benzyl chloride is converted cleanly to toluene quite readily in refluxing THF,[17] but a considerable amount of dimeric product (**16**, **17**) is associated with the reduction of diphenylbromomethane[17,60] or 9-bromofluorene:[17,64]

$$Ph_2CHBr \xrightarrow[THF]{LAH} Ph_2CH_2 + \underset{16}{Ph_2CHCHPh_2}$$

(10)



(11)

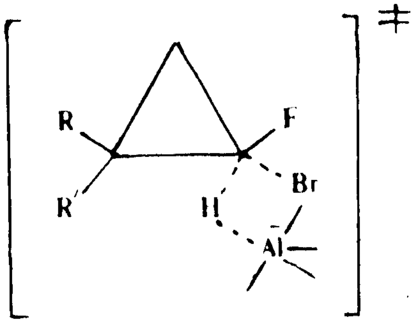
Trevoy and Brown[17] ascribed the formation of the dimers as involving an organometallic compound which came from the parent hydrocarbon product in the presence of excess LAH. That metallation occurred was proved when they mixed fluorene with LAH and then treated the product with carbon dioxide gas to yield fluorene-9-carboxylic acid. Similarly, they argued that diphenylmethane was also liable to metallation since the benzylic protons are acidic. Nonetheless, when Singh and coworkers[64] reinvestigated the reaction with diphenylchloromethane and 9-bromofluorene, a different result was obtained from the control experiments. Instead of carbonation, the mixture of LAH and diphenylmethane or fluorene was subject to treatment with D_2O. They found that the starting material was completely recovered without deuteration. Should an organometallic compound have been formed from the reaction, they reasoned, kinetic isotope effect would favor the removal of a proton instead of a deuteron from the monomer so that deuterated dimer should have been detected. To support their argument, they noted that in Eliel's work[46] on the reaction of α-chloroethylbenzene with a mixture of LAD and LiD, the dimeric product, 2,3-diphenylbutane, was deuterium-free. They also observed ESR active colored species during the course of the reaction of both halides with LAH. The spectra were attributed to the diphenylmethyl and 9-fluorenyl radicals, respectively. Dimer **16** or **17** was found to be the major product. Abstraction of X^+ by hydride ion was deemed unlikely to achieve dimerization. Deprotonation to form a halocarbanion was also ruled out since deuterium was absent in unreacted halide upon D_2O work-up. An electron transfer-hydrogen abstraction mechanism was submitted, with AlH_4^- and $AlH_3^{\cdot}$ being the electron donating species. AlH_3, which could be a by-product, was not considered to be an electon donor as it was found to be inert towards the benzyl halides they examined.

Ashby et al[60] cast doubts on the results of Singh and coworkers.[64] First, they did not obtain the dimeric product, **16**, from the reduction of diphenylchloromethane. When the same procedure was followed, diphenylmethane was produced quantitatively. They did obtain good yield of the dimer with diphenylbromomethane. Second, they demonstrated that AlH_3 was a better electron donor than LAH since a much higher proportion of dimer was formed in the reaction of diphenylbromomethane with AlH_3 than with LAH. However, they maintained that AlH_4^- was directly responsible for electron transfer because the AlH_3 reaction was sluggish and the dimer/monomer ratio was relatively constant throughout the course of the reduction. Unlike Singh and coworkers,[64] they saw no spectroscopic evidence of radical intermediates during the reduction of diphenylhalomethanes. Trityl radical was, however, implied from ESR signals acquired when trityl chloride or trityl bromide was treated with either LAH or aluminum hydride. High deuterium incorporation in triphenylmethane for the reaction with metal deuteride suggests that the stable trityl radical abstracts hydrogen selectively from the reducing agent.

Several cases of dehalogenation of vinylic halides by LAH were mentioned in the literature.[17,51,63,65] From the viewpoint of energetics, it has been estimated[63] that 2-4.3 kcal mol^{-1} is required for the inversion of vinyl radical[66a,66b] whereas the configurationally more stable vinyl anion requires 31.1 kcal mol^{-1} to achieve this process.[66c] Accordingly, the ease of isomerization reflected from product studies may indicate the involvement of radical intermediates. The reaction of trans and cis β-bromostyrenes with LAD was found to be non-stereospecific.[63] This, together with the observation that a significant amount of non-labelled styrene was produced led the authors to the conclusion that the reaction proceeded by a free radical pathway.[63] Higher reaction temperatures (e.g. in refluxing THF) furnished retention products and a polar mechanism was chosen to explain that situation.

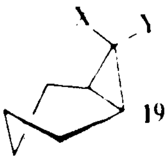
Cyclopropyl substrates are usually unreactive towards nucleophilic attack. S_N2 displacement is geometrically prohibited while an S_N1 process, which requires the formation of a planar carbocation, is also disfavored. Even if the leaving group does depart, the process is usually accompanied by ring opening. Still, the halogen of halocyclopropanes has been known to be replaced by hydrogen in the presence of LAH under mild conditions without ring opening.[68-71] Similarly, bridgehead halides, which normally do not undergo nucleophilic substitution, have been shown to be susceptible to LAH reduction.[72]

Retention of configuration was observed[68] during the course of the reaction of gem-bromofluorocyclopropanes. Bromine was selectively replaced. A four-centered transition state (**18**) was proposed to explain the



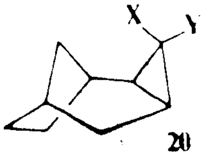
18

stereochemistry of the reaction.[68] Jefford and collaborators[71] also reported overall net retention of configuration at the fluorine-bearing carbon during the selective dechlorination of epimeric 7-chloro-7-fluorobicyclo[4.1.0]heptanes (**19a**, **19b**) in diglyme at 100°. Under the same conditions, *syn* 3-chloro-3-fluorotricyclo[4.2.1.0^{2,4}]nonane (**20a**) gave chiefly the



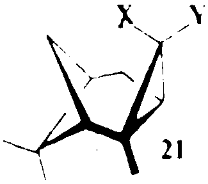
19

a X = F Y = Cl
b X = Cl Y = F
c X = Br Y = Br
d X = H Y = Br
e X = Br Y = H
f X = H Y = H



20

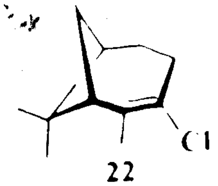
a X = F Y = Cl
b X = Cl Y = F
c X = H Y = F



21

a X = Cl Y = Br
b X = Br Y = Cl
c X = Cl Y = Cl
d X = H Y = Cl
e X = D Y = Cl

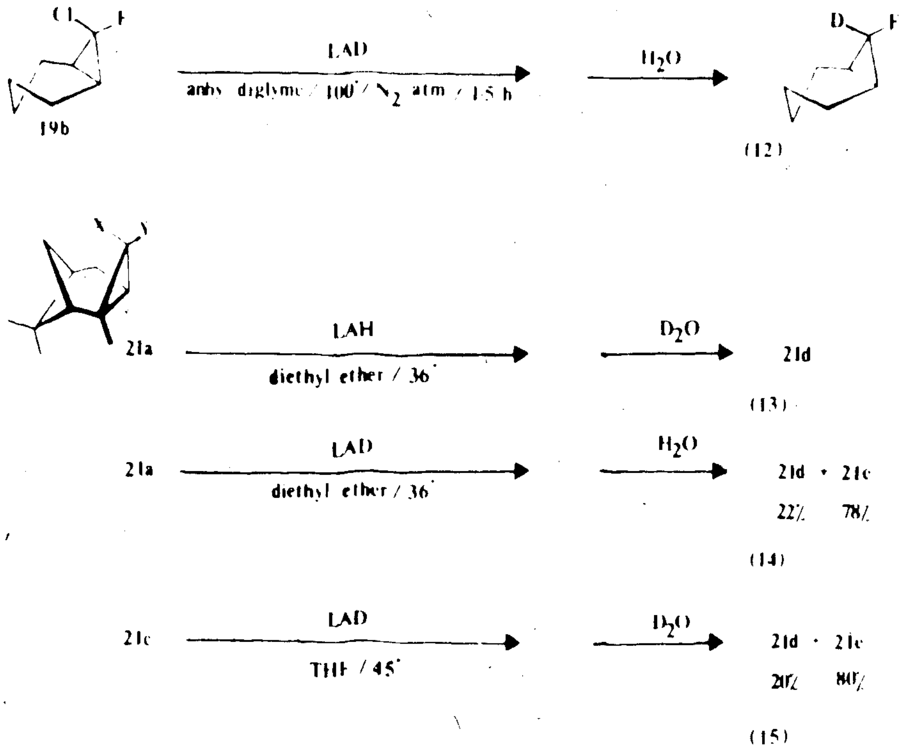
inversion product **20c** while the *anti* isomer (**20b**) afforded mainly the same product, i.e. overall retention of configuration. Concurrently, Hatem and Waegell[69] also observed exclusive inversion for the selective debromination of *syn* 3-bromo-3-chloro-2,7,7-trimethyltricyclo[4.1.1.$0^{2,4}$]octane (**21a**) by the hydride reagent in diethyl ether. Jefford *et al*[71] pointed out that their own results could not be explained by nucleophilic displacement - whether it is S_N1, S_N2 or the 4-centered mechanism. They suggested that the cyclopropyl radical and the cyclopropyl carbanion were possible intermediates which tend to retain their configurations unless any *syn*-disposed substituents in these intermediates encounter intramolecular non-bonded interaction. The high proportion of olefinic product **22** from **21c** as reported by Hatem and Waegell[69] attested to the cyclopropyl ring opening due to steric interaction.



22

To decide whether the radical or the anion was the most likely intermediate, Jefford and coworkers[71] treated **19b** with LAD followed by hydrolysis with H_2O.

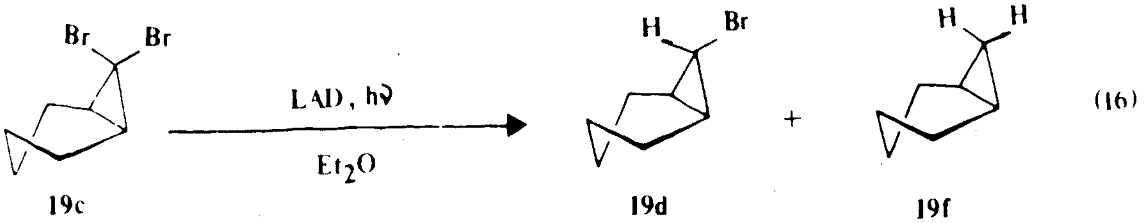
Incorporation of deuterium (100%) was detected at the fluorine bearing cyclopropyl carbon. They inferred the intermediacy of carbanion since they rationalized that a mixture of isotopic products should have been obtained if radicals were involved. A carbanion, they argued, would preferentially capture a deuteron from DCl rather than from the weakly acidic solvent diglyme. Hatem and Waegell also conducted several labelling experiments for the $[4.1.1.0^{2,4}]$ system they studied. The results are summarized in Scheme V along with that of Jefford and coworkers:



Scheme V

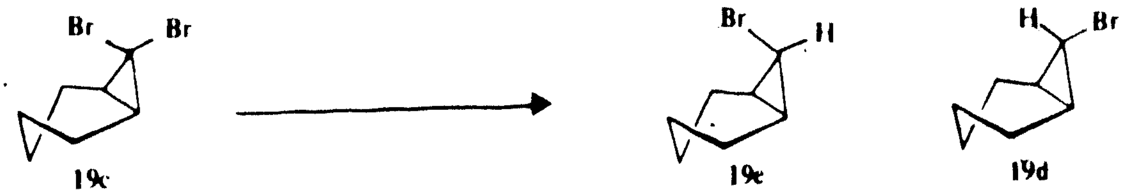
These workers postulated the existence of a cyclopropyl radical intermediate, which rapidly inverts and abstracts hydrogen atom either from the hydride or from the solvent.

Recently Shimizu and coworkers[73] have carried out the photoreductive dehalogenation of aromatic, vinylic and cyclopropyl halides in diethyl ether. They found that the presence of LAH markedly accelerated the reaction. Nevertheless, LAH was not considered to be the source of hydrogen for which the halogen on the substrates exchanged since no deuterium was detected in the products if LAD was used. A considerable amount of 2,3-diethoxybutane was also observed. 7,7-Dibromobicyclo[4.1.0]heptane (**19c**) was one of substrates subject to photoreduction in the presence of LAD.



(16)

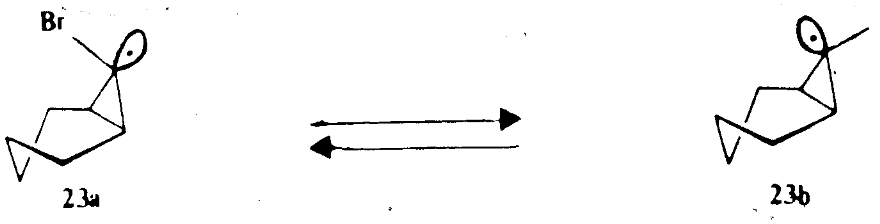
LAH was visualized as an electron donor in the non-chain mechanism they suggested. Debromination of **19c** has been studied utilizing different reagents including LAH,[70] NBH,[74] tri-n-butyltin hydride,[75] methylmagnesium bromide[76] and Na-DMSO.[77] The results of these reactions are outlined in Scheme VI:



Entry	Reagent	Conditions	Overall Yield %	Mole 19e/19d	Reference
(i)	LAH	Et_2O/reflux/18 h	73	3.0	70
(ii)	NBH	DMF/rt /48 h	79	1.8	74
(iii)	$^nBu_3SnH$	neat ?/< 40°/ 2 h	82	2.5	75
(iv)	MeMgBr	THF/rt / 2 h	~72	2.2-2.7	76
(v)	Na-DMSO	DMSO/rt	72	0.11	77

Scheme VI

The ratio of **19e** to **19d** is comparable in every case shown in Scheme VI except that in Entry (v). With sodium borohydride, Groves and Ma[74] have presented evidences to show that radicals were generated at some stage of the reaction in DMF and were involved in a chain process. The reactions of **19c** with the organotin hydride and the Grignard reagent have been established as involving the monobromocyclopropyl radical.[75,76,78] Kuivila[78] had described the reaction with tri-n-butyltin hydride as bromine atom abstraction preceding rapid interconversion between radicals **23a** and **23b**:



(17)

He suggested that steric factor favors abstraction of hydrogen in **23a**, so that **19e**/**19d** is greater than 1. In contrast to the reactions with hydrides and Grignard reagent, the reduction with sodium methylsulfinyl carbanion (Entry (V), Scheme VI) provides the *trans* isomer (**19d**) as the major product. Gardner and coworkers[77] suggested that the latter reaction almost certainly involves nucleophilic displacement on bromine to give a monobromocyclopropyl carbanion which then abstracts a proton from solvent DMSO. In the case of LAH reduction, it appears that the product composition resembles those by other reagents which were believed to participate in radical processes during the debromination of the same starting substrate. Yet Jefford *et al*[71] suggested the intermediacy of carbanion for the dechlorination of **19b** which is structurally related to **19c**.

Hatem and Waegell noted the similarity in the product compositions when **21a** and **21c** were allowed to react respectively with tri-*n*-butyltin hydride and LAH.[69,79] They suggested that radicals were involved in the dehalogenation of **21** effected by either reagent. Selective dehalogenation of dihalocyclopropanes is a characteristic shared by both hydrides;[69-71,74,75,80-82] for example, the selective dechlorinations of **19a** and **19b** to give inversion products were observed with tri-*n*-

butyltin hydride[80] and with LAH.[71] The parallelism between these two reagents is not limited to halocyclopropanes. The stepwise removal of halogen from α,α,α-trichlorotoluene to form toluene suggested by Kuivila[78] might well be compared with similar proposal forwarded by Dibeler[83] for the LAH reduction of a series of halomethanes. Rather vigorous conditions are required for the removal of bridgehead bromine by LAH.[70] Bridgehead halides are equally insensitive to organotin hydrides.[84] On the contrary, vinyl bromides are reduced easily by both reagents, giving high yields.[70,78,81,84] Jefford and coworkers[81] suggested that in the case of the halides of the bicyclo[3.2.1]octenyl system their macroscopic behaviors were similar in the hydrogenolyses of allylic halogen. In the selective removal of vinylic bromine in the same system, however, LAH was found to give mainly allylic rearrangement products while no rearrangment was observed with tri-_n_-butyltin hydride. An approximately 50/50 mixture of _trans_- and _cis_-β-deuteriostyrenes was obtained from the treatment of _trans_-β-bromostyrene either with LAD in Et_2O at room temperature or with tri-_n_-butyltin deuteride in refluxing benzene.[63] A mixture of similar composition was afforded starting from the _cis_ isomer with under the same reaction conditions. Kupchik and Kiesel[84] have shown that isomeric bromostilbenes were reduced by triphenyltin hydride with almost identical stereochemical results. Mechanistically, Blackburn and Tanner[85] have proposed an electron transfer mechanism associated with the propagation chain for the reduction of benzyl iodides with tri-n-butyltin hydride. The sequence has subsequently been confirmed for methyl iodide with triphenyltin hydride.[86] Likewise, Ashby and coworkers[60] have presented pertinent information related to an electron transfer process for the reduction of benzylic and other alkyl iodides by LAH.

It has been commonly accepted[78,85-90] that organic halides are reduced by organotin hydrides via a free radical chain propagation. The reactions can be initiated photochemically, or thermally in the presence of azo and peroxidic initiators.[78,91] They can also be inhibited by hydroquinones.[78,91] Moreover, for a given R group in RX, the reactivity is F < Cl < Br < I and for the same halide, the reactivity follows the order of the stability of the radical R· (i.e. primary < secondary < tertiary).[78,84,89]

Kuivila[92] recognized that the stereochemistry of the reductions of the carbonyl function effected by trialkyltin hydrides differs little from that effected by LAH. While the former reductions may involve homolytic and/or heterolytic cleavage of Sn-H bond,[93-95] polar mechanisms dominate the scene exclusively for the LAH reduction.

Grignard reagents, whose reaction with carbonyl compounds may consist of polar and/or electron transfer processes,[96] resemble the chemical behaviors of LAH in several aspects. One analogy is noted in the product compositions resulted from the reductions of the dibromide **19c** (Entries (iv) and (i), Scheme VI). Gaylord[10] summarized the similarities from early studies: (i) a donor solvent is needed, specifically the ethereal type; (ii) ether cleavage occurs only in the presence of cobalt chloride;[97] (iii) the results of their reactions are similar, as in the conversion of tosylate to hydrocarbon.[98]

Other organometallic compounds and metal hydrides of Groups IIA-IVA have also been reported as being involved in free radical reactions. Hindered *o*-quinones react with the alkyl derivatives of Group IIIA (Al, Ga, In, Tl) to give colored species which are ESR acti[illegible][99] Radical chain mechanisms have been suggested to explain the additions of trialkylboranes[100] and trialkylalanes[101] to the carbon-carbon double bonds of α,β-unsaturated compounds, during the course of which homolytic displacements on the metal centres occur. Substituted aromatic nitrogen-heterocycle are reduced by organoaluminum compounds in the presence of an alkaline metal (e.g. sodium) in THF, and the processes are believed to involve electron transfer.[102]

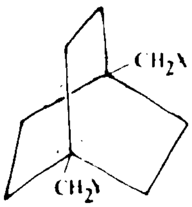
Kochi et al[103] have suggested that free radical chain process could be associated with metal hydride reductions. In addition, they noted that since hydrogen is an excellent σ-donor ligand, metal hydrides are able to participate as electron donors. Thus, the alkyl derivatives of the deuterides of boron, aluminum and tin have been shown to transfer deuterium atoms to either endo or exo norbornyl-2-mercuric bromide to furnish a common mixture of exo and endo norbane-2-d irrespective of the metal deuteride used.[104] Lithium triethylborohydride, which is probably the strongest known nucleophile,[105,106] has most recently been reported as donating single electron and hydrogen atom to cyclizable alkyl iodides and bromides.[107]

In the case of LAH reduction, radical processes have been considered for other organic substrates besides certain aromatic, benzylic, vinylic and cyclopropyl halides. Most of the investigations of this kind owed much to the efforts of Ashby and his colleagues. In recent years they have presented documentation of single electron transfer (SET) in the reactions of alkyl halides,[60,107-111] ketones,[111-114] alcohols[115] and conjugated hydrocarbons[111,116] with a variety of metal hydrides, alkoxides of lithium and aluminum, as well as lithium amides. Their methodology comprises ESR studies, product studies of cyclizable probes, employment of radical traps and stereochemical studies. This is epitomized in their examinations of the reactions of alkyl halides, some results of which have been presented above.

For example, trityl radical detected from ESR studies, could be generated from the reactions of trityl chloride and bromide with HMgCl, HMgBr, MgH_2,[60,109,110] lithium tetrakis(N-dihydropyridyl)aluminate (LDPA)[111] and lithium diisopropylamide[114] in addition to LAH and AlH_3.[60,109,110] The probes they chose for studying the reductions of alkyl halides consisted of the cyclizable 5-hexenyl moiety. Cyclopentyl products were obtained in considerable amounts when the iodides were treated with LAH. Labelling experiments revealed that the hydrogen atom from the radical trap dicyclohexylphosphine, if present, was incorporated partially into both the cyclization and the straight-chain products. The intermediacy of radicals was substantiated by stereochemical studies. They found that (+)-2-iodooctane was reduced by LAD in THF with much less stereospecificity than the corresponding reaction with bromides, chlorides and tosylates. In the case of the bromides, probably both

S_N2 and SET act simultaneously, the extent of which depends largely on the steric environment of the substrate and the stability of the corresponding alkyl radical. Hence, cyclization was found in the LAH reduction of 1-bromo-2,2-dimethyl-5-hexene, albeit in small amount, but not in 6-bromo-1-hexene. Net inversion of configuration was observed for the hydrogenolysis of 2-bromooctane by LAD. In the cases of chlorides and tosylates, no cyclization products were detected for the reactions of cyclizable substrates with LAH and with AlH_3. This, together with the observation that inversion products were obtained from the LAD reduction of optically active 2-chlorooctane and 2-octyl p-toluenesulfonate, led them to exclude radicals as intermediates.

Nevertheless, the occurrence of carbon-carbon cleavage during the course of the LAH reduction of sulfonates **24** in THF, hexamethylphosphoramide (HMPA) or

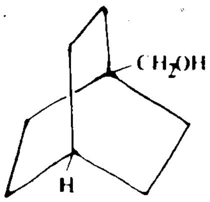


24

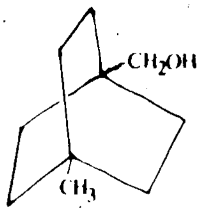
a X=OTs Y=OTs

b X=OTs Y=OH

c X=OMs Y=OMs



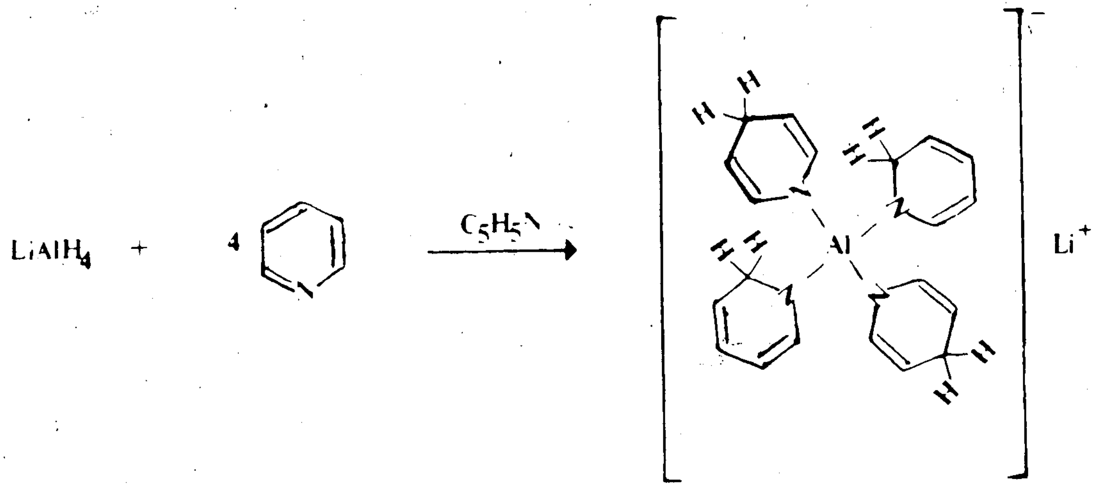
25



26

THF-HMPA has been considered as a diagnosis of electron transfer.[117] Compound **25** was formed in 1-19% as a combined result of carbon-carbon and sulfur-oxygen bond cleavages of **24**. This was anomalous since LAH reduction of sulfonates, which is generally accepted as an S_N2 process, furnishes the corresponding hydrocarbons.[48,49,118-120] Parent hydrocarbons of **24a** and **24c** were not obtained at all from the reaction, although the normal carbon-oxygen bond cleavage still occurred as **26** was produced in considerable amount for most cases.[117,121] The ratio of S-O to C-O bond cleavages was found to be solvent dependent.[117]

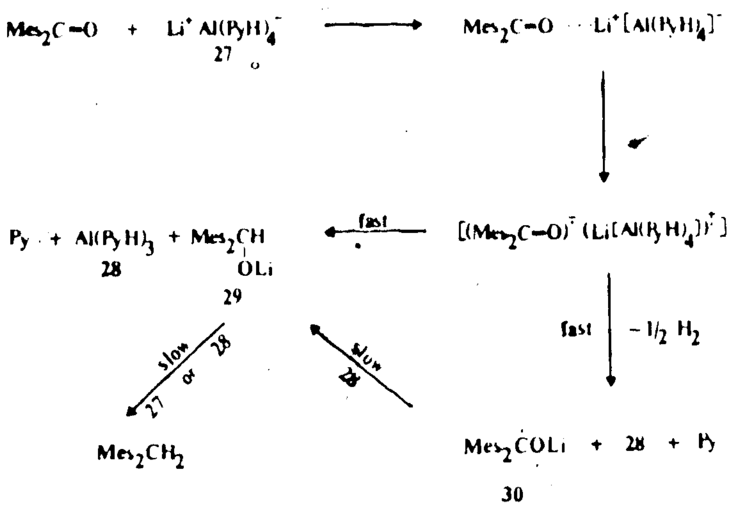
ESR active species were detected during the course of the reductions of hindered aromatic ketones with HMgX, B_2H_6, MgH_2, AlH_3,[112] lithium alkoxides, aluminum isopropoxide,[113] lithium amides[114] and LDPA (**27**).[111] The latter reagent is prepared from LAH and pyridine:[122]



27

(18)

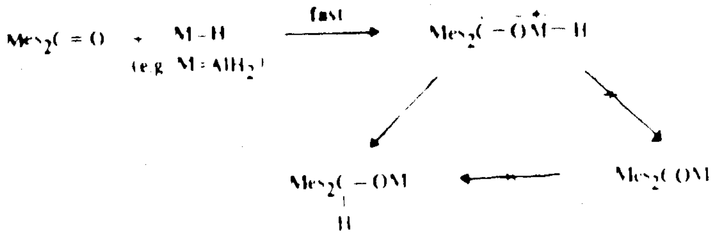
Single electron transfer from the reagent to the carbonyl function was suggested for each case. A ketyl radical anion was inferred for the reactions of dimesityl ketone (DMK) with LDPA and with HMgBr. In the latter case, the ESR signal observed for the radical intermediate was found to be similar to that of the free ketyl generated when DMK was mixed with tert-butylmagnesium bromide. Likewise, the ESR active species generated from the reaction of DMK with LDPA was found to be identical to that of the lithium ketyl prepared independently. In addition to the ketone, 87% dimesitylmethanol and 5% dimesitylmethane were detected in the product mixture. The hydrocarbon product was shown to be derived from a further reaction of lithium dimesitylmethoxide (**29**) with LDPA and the by-product $Al(PyH)_3$ (**28**) since the same product was obtained when the independently prepared alkoxide was treated with LDPA and $Al(PyH)_3$ respectively. The alkoxide itself was believed to come either from the radical cation-radical anion pair by hydrogen radical transfer, or to a much lesser extent, from the reaction of the free ketyl and $Al(PyH)_3$. The radical pair might also lose a hydrogen radical, either by self coupling or by hydrogen abstraction from THF solvent, giving rise to the free ketyl. The proposed mechanism is reproduced in Scheme VII below:



Scheme VII

The slow decay of the intensity of the ESR signal due to the free ketyl **30** was attributed possibly to its reaction with 28.

The paramagnetic species was shown not to be the ketyl for the reductions of aromatic ketones with the other reagents because of different ESR signals.[112-114] Moreover, the ketyls generated from DMK and benzophenone have been shown not to abstract hydrogen from solvent THF nor from the metal hydride. Yet a 100% yield of dimesitylmethanol was produced from DMK versus AlH_3. The ESR signal obtained during the metal hydride reduction of DMK was suggested to be that of the radical cation-radical anion pair, $Ar_2\dot{C}-\overset{+}{\bar{\dot{O}}}MH$. With AlH_3, the alcohol product was formed continuously during the entire course of the reaction and its yield increased in a first order fashion after the ESR and visible absorption reached a maximum. It was suggested that the alcohol product was derived from the radical pair. The following mechanistic scheme was proposed:[112]



Scheme VIII

The production of hydrocarbon from **29** with **27** or **28** (Scheme VII) parallels the conversion of benzhydrols, trityl alcohol and 2,2,4-trimetyl-3-pentanol to their parent hydrocarbons in the presence of LAH.[115] Again, the latter reaction was believed to proceed _via_ an electron transfer process. ESR active species were detected, accompanied by the development of an orange-red coloration in the solutions. In the case of trityl alcohol, the ESR spectrum was found to be consistent with that of the trityl radical. The concentration of the radicals was solvent dependent; usually a maximum of 10-20% was estimated in THF and much less in diethyl ether. The products were also formed much more readily in the latter solvent. Experiments of dimesitylmethanol and trityl alcohol with LAD afforded about 10% non-deuterated hydrocarbons, the remainder being the monodeuterated analogs. This was interpretated as further evidence for the presence of a radical intermediate which abstracts hydrogen preferentially from the metal hydride reagent.

It is not surprising that polynuclear aromatics and other highly conjugated hydrocarbons[111,116,123] and aromatic nitrogen heterocycles[123,124] accept single electrons from LAH. Gause and Rowlands,[123] who were probably the first authors to mention electron transfer by LAH, recorded the ESR and visible spectra of some common highly conjugated unsaturated hydrocarbons and heterocycles. They noted that the ESR signal of the paramagnetic species from naphthacene was identical to that produced from sodium metal reduction.[125] Ashby and coworkers[111,116] also detected ESR active species when polynuclear aromatic hydrocarbons were mixed with LDPA, LAH, AlH_3, MgH_2 or HMgCl. It appears that the radical anion $Ar^{\overline{\cdot}}$ disproportionates to Ar^{2-} and Ar or remains as $Ar^{\overline{\cdot}}$ instead of abstracting hydrogen from the radical cation since the treatment with LAD and then with H_2O was found to give much more ArH_2 than ArHD. Similarly, Kaim[124] was able to demonstrate SET by LAH to pyrazine, quinoxaline and 4,4'-bipyridine with the aid of ESR and UV techniques. The ESR signal corresponds either to a coordination complex of the radical anion with lithium or with aluminum. By comparing the ESR coupling constants with those from the diethylaluminum complexes of the nitrogen-heterocycles he studied, he concluded that pyrazine co-ordinates with 2 Li^+, one for each nitrogen of the compound while each of quinoxaline and 4,4'-bipyridine coordinates with 2 AlH_2^+, again one for each nitrogen of the compound.

Finally, LAH has been proved to reduce organoiron cation in THF or in dimethoxybutane by single electron transfer preceding hydrogen atom transfer, rather than nucleophilic hydride attack.[126,127] The electron transfer intermediates have been characterized by ESR[126,127] and Moessbauer[127] spectroscopies at low temperatures.

I.2 Proposal

One of the most important mechanistic questions concerning the hydride reductions is to differentiate between hydride transfer and electron transfer-hydrogen atom abstraction sequence of the processes. Homolytic pathways have been suggested for a number of metal hydride reductions. It is worthy to look into the mechanism of the most common of these, namely, the LAH reduction, for substrates which are capable of being reduced heterolytically or homolytically.

There have been ample mechanistic suggestions that LAH reduction either proceeds via hydride transfer or involves radical intermediates. The electron transfer-hydrogen atom abstraction sequence is usually implied for the latter alternative. Recognizing AlH_4^- as a good nucleophile[10,20,106a] is the necessary condition for the hydride transfer mechanisms. Recognizing AlH_4^- as a good electron donor is the prerequisite for the electron transfer mechanisms.[60,62,73,126] Probably it may act as both nucleophile and electron donor simultaneously, the degree of which character depends largely on the substrate and to a lesser extent, on the solvent,[120] the choice of which is rather limited.

The parallelism in the macroscopic chemical behaviors between LAH and organotin hydrides has been noted; in particular, both can engage in polar and radical processes. A probe known to react with an organotin hydride reagent via either path might react similarly with LAH.

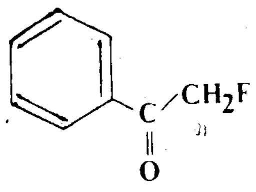
Tanner and coworkers[128] have recently proposed a radical chain mechanism for the initiated homolytic reductions of cyclopropyl phenyl ketone, α,α,α-trifluoroacetophenone and α-fluoroacetophenone by triphenyltin hydride. They have provided evidence which indicated that an electron transfer step was operative in the chain sequence for the two fluoroketones. α-Fluoroacetophenone reacts to give a defluorinated product, acetophenone, as the product of electron transfer.

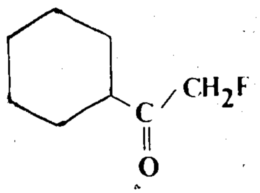
It was of interest to study the mechanistic paths of the reaction of the α-haloketone, α-fluoroacetophenone, with LAH. On the other hand, it would be of comparative value to examine the corresponding reaction of an aliphatic α-fluoroketone since the absence of an aromatic structure limits to some extent the possibility of radical pathways.

The companion reaction with aluminum hydride might provide different results in accord with the differences in chemical behaviors of LAH and AlH_3. Consequently, the reaction of α-fluoroketones with aluminum hydride was also investigated.

RESULTS

The ketones chosen for study were α-fluoroacetophenone (I) and cyclohexyl fluoromethyl ketone (VI).


I

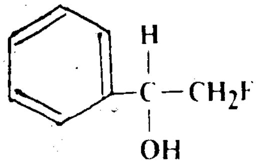

VI

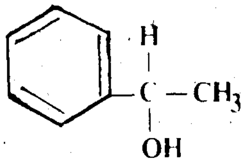
The reactions with LAH and aluminum hydride respectively were carried out in THF, and in order to compare the results of the reaction with those of the corresponding organotin hydride reaction of I,[95,128] the LAH reduction in solvent benzene was also examined. Solutions of LAH and of aluminum hydride were employed for the reactions in THF. The solution of aluminum hydride was prepared from an LAH solution using a calculated amount of sulfuric acid.[2]

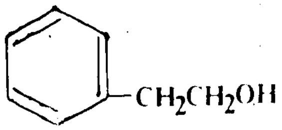
II.1 The Reaction of α-Fluoroacetophenone (I) with Lithium Aluminum Hydride

Exploratory studies in solvent benzene showed that three products were yielded: 2-fluoro-1-phenylethanol

(II), 1-phenylethanol (III) and 2-phenylethanol (IV). Analogous studies in solvent THF afforded comparable


II


III


IV

results, although IV was only formed in trace quantity. Unhydrolyzed reaction mixtures, in either solvent, were analyzed by glpc. It was found that the same products were detected as with the corresponding hydrolyzed mixtures. Styrene oxide, which might be produced from the reaction, was treated with aqueous sulfuric acid (the hydrolytic procedure) using synthetic sample in both THF and benzene. It was shown to be inert.

The product composition of the reaction was investigated as a function of the mole ratio of the hydride to the ketone, keeping the concentration of the latter relatively constant. The results are shown in Table I. In both solvents, the yield of the fluoroalcohol II exhibited a maximum quantity while the defluorinated alcohol III increased with the amount of LAH. In solvent THF, at approximately 1:1 mole ratio, III was produced almost exclusively. On the other hand, its isomer, IV, was at

Table I

Reaction of α-fluoroacetophenone (I) with various quantities of lithium aluminum hydride (LAH) at 61°[a,b]

Reaction	[I],M	Mole LAH/I	Reaction Medium	Product, Yield %[c]			Unreacted Ketone	Material Balance, %[c]
				$PhCH(OH)CH_2F$	$PhCH(OH)CH_3$	$PhCH_2CH_2OH$		
1	0.22	0.23	Benzene	34.8	0	0	61.1	95.9
2	0.22	0.47	Benzene	49.7	6.1	25.4	6.2	$\gtrsim$100.0[d]
3	0.22	0.80	Benzene	14.4	51.2	24.1	1.2	89.7
4	0.22	1.0	Benzene	7.1	74.9	17.8	0	99.8
5	0.22	2.1	Benzene	0.5	76.7	23.0	0	100.2
6	0.17	0.24	THF	39.6	0.4	0	58.8	98.8
7	0.17	0.49	THF	54.8	45.9	0.7	0	103.1
8	0.17	0.97	THF	5.8	92.6	0	0	98.4
9	0.17	1.5	THF	1.4	96.8	0	0	98.2
10	0.15	0.49	Benzene	32.3	11.3	30.9	7.0	88.0[e]
11[f]	0.15	0.49	Benzene	22.0	49.7	26.7	0	96.4
12	0.15	0.49	THF	51.9	43.6	1.0	0	96.5

[a] Slurry of LAH in benzene was used without stirring. When THF was the reaction medium, solution of the hydride reagent was employed.

[b] The reaction ampoules were degassed, sealed and thermostated before mixing the materials. The reaction period was 16 h in each case.

[c] This is based on the starting mmole of I.

[d] 12.6% Acetophenone and traces of phenylacetaldehyde were also detected and are included in the material balance.

[e] 6.5% acetophenone was also detected and is included in the material balance.

[f] The solvent of 1 mL THF solution of LAH was removed under reduced pressure and replaced by 1 mL distilling benzene. The source of the solution was the same as that for reaction 12.

most barely detectable in the same medium. In benzene, its yield remained fairly constant at about 20% beyond a 1:2 mole ratio of hydride-to-substrate. At about this ratio, acetophenone and traces of phenylacetaldehyde were also detected in the product mixture.

Since it appeared that the defluorinated products may have been formed at the expense of the fluoroalcohol II, a study of the product composition at various reaction times was carried out. The results of the study are presented in Table II. In either reaction medium, II was rapidly generated and thereafter its yield declined. The disappearance of II was accompanied by the build-up of alcohol III in THF (Reactions 11-14) and by both III and IV in benzene (Reactions 3-8). In the latter case, agitating the slurry of LAH during the course of the reaction decreased the yield of IV in favor of that of III (Reactions 5 and 9, 6 and 10).

The fluorohydrin II was prepared independently and allowed to react with the hydride reagent under the same conditions. Table III lists the variation of product composition with time for the reduction of this compound. The reaction in benzene was conducted in the atmosphere since it had been found that the reaction of ketone I was unaffected by the presence of air. Alcohols III and IV were indeed obtained and in THF, compound IV was formed, at most, in traces.

Table II

Reaction of α-fluoroacetophenone (I) with lithium aluminum hydride at various times at 61°[a,b]

Reaction	[I],M	Mole LAH/I	Reaction Medium	Reaction Period, h	Product, Yield %[c]				Material Balance, %[c]
					$PhCH(OH)CH_2F$	$PhCH(OH)CH_3$	$PhCH_2CH_2OH$	Unreacted Ketone	
1	0.22	0.89	Benzene	0.017	3.2	0	0.5	96.3	100.0
2	0.22	0.91	Benzene	0.083	49.2	0	0.9	50.7	100.8
3	0.22	0.91	Benzene	0.25	94.9	1.8	1.3	1.9	99.9
4	0.22	0.90	Benzene	1	87.1	9.1	2.5	0	98.7
5	0.22	0.89	Benzene	3	65.7	25.6	12.9	0	104.2
6	0.22	0.94	Benzene	8	16.7	57.0	26.6	0	100.3
7	0.22	0.93	Benzene	16	2.5	62.4	36.8	0	101.7
8	0.22	0.91	Benzene	42	1.2	65.4	30.8	0	97.4
9[d]	0.22	0.94	Benzene	3	26.1	61.3	7.6	0	95.0
10[d]	0.22	0.93	Benzene	8	4.6	81.0	11.5	0	97.1
11	0.17	0.49	THF	0.017	93.5	1.3	0	3.4	98.2
12	0.17	0.49	THF	0.25	94.8	6.7	0	0	101.5
13	0.17	0.49	THF	3	85.1	18.0	traces	0	$\gtrsim$103.1
14	0.17	0.49	THF	16	54.8	45.9	0	0	101.4

[a] Slurry of LAH in benzene was used without stirring unless otherwise specified. When THF was the reaction medium, solution of the hydride reagent was employed.

[b] The reaction ampoules were degassed, sealed and thermostated before mixing the materials.

[c] It is based on the starting mmole of I.

[d] The reaction mixture was stirred throughout the reaction period.

Table III

Reaction of 2-fluoro-1-phenylethanol (II) with lithium aluminum hydride at various times at 61°[a]

Reaction	[II],M	Mole LAH/II	Reaction Medium	Reaction Period, h	Product, Yield %[b]			Material Balance, %[b]
					$PhCH(OH)CH_3$	$PhCH_2CH_2OH$	Unreacted Alcohol	
1	0.21	0.96	Benzene	0.25	traces	0	101.7	≥101.7
2	0.21	0.96	Benzene	1	7.7	0	93.2	100.9
3	0.21	0.96	Benzene	2	35.1	1.4	57.8	94.3
4[c]	0.21	0.96	Benzene	2	37.1	3.8	55.0	95.9
5[d]	0.21	0.98	Benzene	2	33.3	2.1	62.0	97.4
6	0.21	0.96	Benzene	4	66.6	2.8	26.8	96.2
7	0.21	0.96	Benzene	6	95.2	4.0	7.4	106.6
8	0.21	0.96	Benzene	10.5	97.7	4.6	2.4	104.7
9[c]	0.21	0.90	Benzene	16	57.5	26.8	11.8	96.1
10[d]	0.22	0.86	Benzene	17	65.7	24.2	8.8	98.7
11[c]	0.15	1.6	THF	0.5	29.5	0	70.9	100.4
12[c]	0.15	1.6	THF	1	49.9	0	45.6	95.5
13[c]	0.15	1.6	THF	3	86.7	traces	6.3	93.0
14[c]	0.15	1.6	THF	8	89.7	traces	3.4	93.1

[a] The reaction in benzene, was carried out, with stirring, in a reaction flask which was open to the atmosphere.

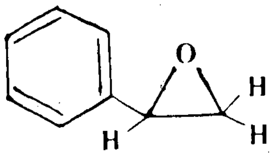
[b] It is based on the starting mmole of II.

[c] The reaction ampoules were degassed, sealed and thermostated before mixing the materials.

[d] The reaction was carried out, without stirring in a sealed reaction ampoule which was not degassed.

LAH used in the reaction in the aromatic solvent was employed without further purification as lithium hydride, the principal impurity in commercial LAH, was found to be unreactive toward I and II (see Experimental). An examination of the reaction using purified LAH and non-purified one in benzene revealed that the only genuine difference was in the higher rate of the production of alcohol III with the purified reagent (Reactions 10 and 11, Table I).

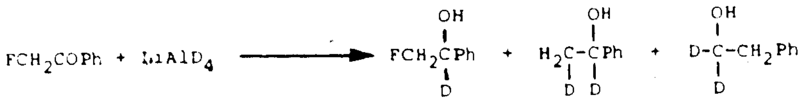
The reactions of both ketone I and fluoroalcohol II with lithium aluminum deuteride (LAD) were carried out in order to gain further insight into the mechanism by which the defluorinated products were formed. Since the intermediacy of an epoxide has been suggested for the dehalogenation of certain halohydrins by LAH[38,130,143(c)] and also for the production of IV from the reaction of I with aluminum isopropoxide,[136] the possibility of styrene oxide (V) as an intermediate was investigated by carrying out its reduction with LAD in benzene and in THF. The results of these tracer experiments are listed in Table IV. Figures 1 and 2 show the ^{1}H and ^{2}H nmr spectra for the product mixtures resulted from the LAD reaction in benzene of compounds I and II, respectively.



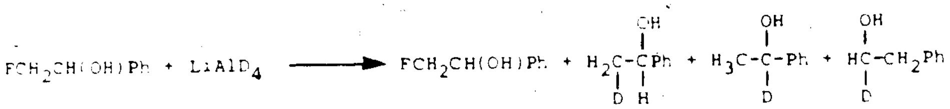
V

Table IV

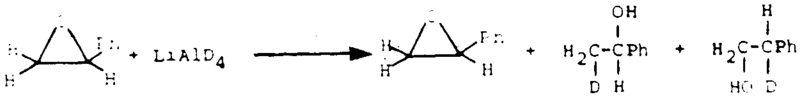
Reactions of α-fluoroacetophenone (I), 2-fluoro-1-phenylethanol (II) and styrene oxide (V) with lithium aluminum deuteride (LAD) at 61°[a-c]



	[I],M	Mole LAD/I	Reaction Medium	Product composition, %[d]		
(1)	0.20	0.65	Benzene	35.2	33.1	31.7
(2)	0.18	0.70	THF	17.9	82.1	(traces)[e]



	[II],M	Mole LAD/II	Reaction Medium	Product composition, %[d]			
(3)	0.33	0.72	Benzene	40.5	31.1	1.4	27.0
(4)	0.14	0.69	THF	26.7	73.1	0	(traces)[e]



	[V],M	Mole LAD/V	Reaction Medium	Product composition, %[d]		
(5)	0.39	0.54	Benzene	37.5	39.6	22.9
(6)	0.17	0.51	THF	0	95.0	5.0

---

[a] Slurry of LAD in benzene was used without stirring. When THF was the reaction medium, solution of the deuteride reagent was employed.

[b] The reaction ampoules were degassed, sealed and thermostated before mixing the materials. The reaction period was 16 h in each reaction and the reaction mixture was worked up by treating with H_2SO_4-H_2O.

[c] The structures of the products were elucidated from their ^1H and ^2H nmr spectra.

[d] This is based on a combination of the molar ratios from glpc analysis and ^1H and ^2H nmr integrations.

[e] Glpc analysis showed the presence of 2-phenylethanol. This was not detectable from nmr analyses.

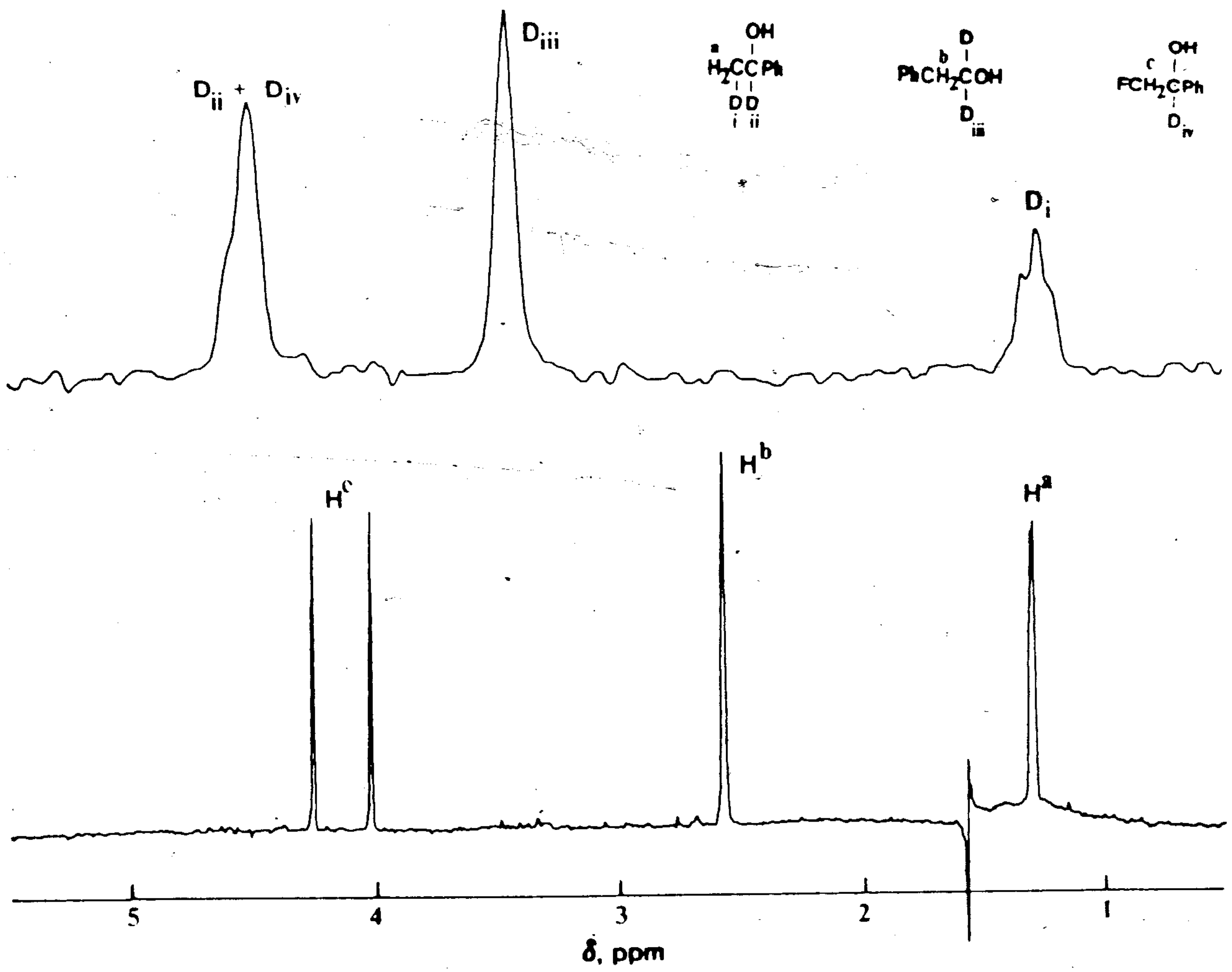


Figure 1. 200 °MHz ^1H (bottom) and ^2H NMR Spectra of the product mixture from the reaction of α-fluoroacetophenone with LAD in benzene

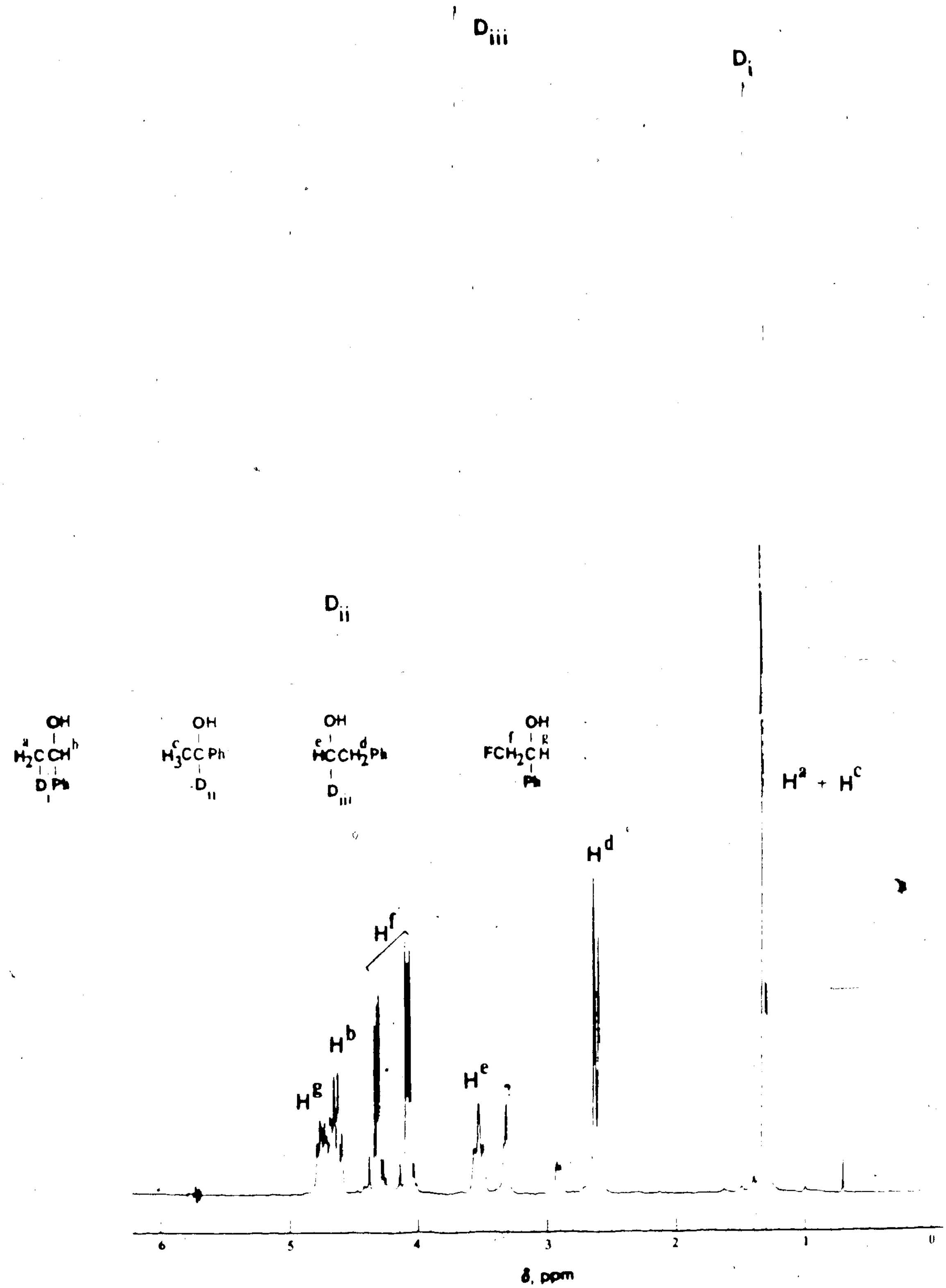


Figure 2. 200 MHz ^1H (bottom) and ^2H NMR Spectra of the product mixture from the reaction of 2-fluoro-1-phenylethanol with LAD in benzene (? is probably H_2O).

The effects of an added radical initiator (α,α'-azobisisobutyronitrile, AIBN), radical inhibitor (dinitrobenzenes, p-DNB and m-DNB; 1,4-dicyanobenzene, DCB; dicyclohexylphosphine, DCPH) or oxygen on the reaction was examined. The results are shown in Table V. AIBN exhibited little influence on the product composition of the reaction in benzene. Likewise, DCPH, which is a common radical trap, only affected the yield of each product slightly. In the same reaction medium, 4-7% of either m-DNB or DCB significantly reduced the product yields of alcohols III and IV. The formation of the fluoroalcohol II from the fluoroketone was unaffected. The defluorinated carbonyl compounds, acetophenone and phenylacetaldehyde, were also produced from the reactions carried out in the presence of an inhibitor. The amount of unreacted DCB in the product mixture was determined by glpc analysis. At least 60% of this material remained after the reaction. m-DNB was not detectable under the analytical condition employed, yet the extent of suppressing defluorination appeared to be comparable to the action of DCB. Earlier, it was noted that stirring enhanced the formation of alcohol III in the heterogeneous medium. When the same sort of treatment was used during the reaction of I in the presence of m-DNB, no

Table V

Reactions of α-fluoroacetophenone (I) and 2-fluoro-1-phenylethanol (II) with lithium aluminum hydride (LAH) at 61° in the presence of additives[a,b]

(A) Reaction in Benzene[c]

Reaction	Substrate[d]	Mole LAH/ Substrate	Additive, %[e]	Product, Yield %[e]						Material Balance, %[e]
				FCH_2COPh	$FCH_2CH(OH)Ph$	CH_3COPh[f]	$CH_3CH(OH)Ph$	$OHCCH_2Ph$[f]	$HOCH_2CH_2Ph$	
1	I	1.0	-	0	7.1	0	74.9	0	17.8	99.8
2	II	1.1	m-DNB,[g] 3.8	1.9	90.0	0.1	1.8	0.3	1.4	96.5
3	I	1.2	m-DNB,[g] 6.7	2.6	86.4	0.3	0.9	0.3	1.1	91.6
4[h]	I	1.1	m-DNB,[g] 3.7	0.8	85.5	0.4	1.5	0.4	2.2	90.8
5	I	1.0	DCB,[g,i] 4.0	2.6	86.5	traces	0.6	1.5	0.7	$\gtrsim$92.1
6	I	1.1	DCB,[g,j] 5.9	0.4	92.3	traces	1.2	0.7	1.3	$\gtrsim$95.9
7	I	1.0	DCPH,[g] 4.1	3.0	12.2	2.5	51.3	0.7	24.1	93.8
8	I	0.95	DCPH,[g] 5.5	7.7	15.7	2.3	54.9	traces	11.7	$\gtrsim$92.3
9	I	1.1	AIBN,[g] 4.4	0	7.0	0	74.0	0	12.6	93.6
10	II	0.90	-	-	11.8	0	57.5	0	26.8	96.1
11	II	0.91	m-DNB,[g] 3.8	-	99.9	0	0.2	0	0.1	100.2
12	II	0.92	DCB,[g,k] 4.0	-	98.1	0	0.3	0	0.2	98.6
13	II	0.94	DCPH,[g] 4.1	-	12.1	0	65.4	0	21.3	98.8
14	II	0.82	-	-	17.6	0	55.9	0	24.6	98.1
15[m]	II	0.83	AIBN,[g] 5.8	-	23.2	0	47.5	0	28.8	99.5

continued.....

Table V (continued):

(B) Reaction in THF

Reaction	Substrate[n]	Mole LAH/ Substrate	Additive, %[e]	Reaction Period, h	Product, Yield %[e]				Material Balance, %[e]
					FCH_2COPh	$FCH_2CH(OH)Ph$	$CH_3CH(OH)Ph$	$HOCH_2CH_2Ph$	
1	I	0.49	-	0.017	3.4	93.5	1.3	0	98.2
2	I	0.49	p-DNB,[g] 4.0	0.017	2.5	94.4	0.8	0	97.7
3	I	0.49	-[o]	0.017	4.4	90.4	0	0	94.8
4	I	0.49	-[r]	16	0	54.8	45.9	0.7	101.4
5[p]	I	0.49	p-DNB,[g] 4.0	16	0	89.1±0.5	7.0±0.7	1.0±0.1	97.1±0.4
6	I	0.65	-[q]	19	0	13.3	92.0	1.5	106.8
7	I	0.65	-[o,r]	19	0	51.8	47.7	0.5	100.0
8	I	0.65	DCB,[g,s] 5.7	19	0	29.0	63.1	traces	≳92.1
9[p]	II	0.63	-[t]	19	-	25.3±2.3	72.6±3.9	1.4±0.8	99.3±0.1
10[p]	II	0.63	m-DNB,[g,t] 4.0	19	-	56.9±4.7	38.1±5.2	0.9±0.1	95.9±0.4
11[p]	II	0.63	DCB,[g,s] 5.8	16	-	78.8±9.7	24.5±9.9	traces	103.2±0.2
12	II	0.63	-[o,u]	19	-	47.4	47.9	traces	≳95.3
13	II	1.6	-	3	-	5.4	94.6	1.5	101.5
14	II	1.6	-[o]	3	-	7.9	87.8	0	95.7
15	II	1.6	m-DNB,[g] 4.0	3	-	5.2	97.0	1.1	103.3

continued.....

Table V (continued): Footnotes

[a] Slurry of LAH in benzene was used without stirring. Whenever the reaction was carried out in THF, solution of the hydride reagent was employed.

[b] The reaction ampoules were degassed, sealed, and thermostated prior to mixing of the materials, unless otherwise specified.

[c] Reaction period was 16 h unless otherwise specified.

[d] The initial concentration of the substrate was 0.21-0.22 M.

[e] This is based on the mmole of the starting substrate.

[f] It was identified and quantified by a combination of glpc, glpc-ms and glpc-ir analyses.

[g] m-DNB = 1,3-dinitrobenzene; DCB = 1,4-dicyanobenzene; DCPH = dicyclohexylphosphene; AIBN = α,α'-azobisisobutyronitrile; p-DNB = 1,4-dinitrobenzene.

[h] The reaction was carried out, with stirring, in a reaction flask which was open to the atmosphere.

[i] By glpc analysis, 3.3% (relative to starting mmole of substrate) DCB remained after the reaction.

[j] By glpc analysis, 3.5% (relative to starting mmole of substrate) DCB remained after the reaction.

[k] By glpc analysis, 3.6% (relative to starting mmole of substrate) DCB remained after the reaction.

[l] Reaction period was 17 h.

[m] Reaction period was 19 h.

[n] The initial concentration of the substrate was 0.15-0.17 M.

[o] The reaction ampoule was sealed, without degassing, and thermostated before mixing the materials.

[p] This is the average result of two experiments.

[q] When the reaction mixture was treated with 16% (relative to starting mmole of substrate) cyclohexanone for 1 h, mole cyclohexanone/cyclohexanol = 0.79.

[r] When the reaction mixture was treated with 16% (relative to starting mmole of substrate) cyclohexanone for 1 h, all cyclohexanone was recovered.

[s] By glpc analysis, no DCB remained after the reaction.

[t] The reaction mixture was treated as in footnote r, but with 10% ketone. All cyclohexanone was consumed.

[u] The reaction mixture was treated as in footnote t. Mole cyclohexanone/cyclohexanol = 0.49.

significant difference was observed compared with non-agitating reaction mixture (Reactions 2 and 4, Series (A), Table V). ~~In THF~~ (Series (B), Table V), the presence of DCB or DNB also reduced the yield of the defluorinated alcohol III, but not as much as it did in benzene. In one case with *p*-DNB (Reaction 5), exce[illegible]ydride sufficient to reduce 18 mol% added cyclohexano[illegible]s available after 19 h of the reaction of the ketone substrate, despite a lower yield of the defluorinated product. All the added DCB was consumed during the course of the reaction of I or II with the hydride reagent. No dehalogenated carbonyl products were detected.

Like in benzene, the conversion of I to II was not affected by oxygen in THF (Reactions 1 and 3, Series (B), Table V). Unlike the reaction carried out in benzene, the dehalogenation of II gave lower yield of alcohol III under undegassed conditions in the ethereal solvent. When cyclohexanone was added to reaction mixtures after 19 h, less cyclohexanol was detected for the undegassed reactions (Reactions 6 and 7, 9 and 12). With excess LAH, the disparity between degassed and undegassed reactions was insignificant.

To be certain that the products of the reaction, III and IV, were not isomerized by the action of excess hydride, control experiments with LAH were carried out on these materials. Under the reaction conditions (degassed/61°/16 h), isomerization did not occur either in benzene or in THF. Furthermore, the reduction of acetophenone in benzene furnished only product III.

II.2 The Reaction of α-Fluoroacetophenone (I) with Aluminum Hydride in Tetrahydrofuran

Preliminary examination of the reaction revealed the formation of fluoroalcohol, II, 1-phenyl- and 2-phenylethanols (III and IV) along with acetophenone and phenylacetaldehyde. Increasing the mole ratio of aluminum hydride to the ketone substrate (I) to 1:1 eliminated the latter products completely (see Table VI). The product alcohol IV predominated at low hydride-to-substrate ratios and decreased to about 2% at the highest ratio employed. The decrease paralleled the rise in the yield of alcohol III. Unlike the LAH reaction, it was not clear, from varying the hydride-to-substrate ratio, whether defluorination of II accounted, at least partially, for the formation of the other alcohols. A time study of the reaction showed that II was produced rapidly in the first minute and was subsequently consumed while defluorinated alcohols accumulated simultaneously.

Table VI

Reaction of α-fluoroacetophenone (I) with various quantities of aluminum hydride in THF at 61°^{a}

Reaction	Mole^b AlH_3/I	Reaction Period,h	Product, Yield %^{c}				Unreacted Ketone	Material Balance, %^{c}
			$PhCH(OH)CH_2F$	$PhCOCH_3$	$PhCH(OH)CH_3$	$PhCH_2CH_2OH$		
1	0.32	16	26.6	2.7	traces	1.7	61.5	≥92.5^d
2^e	0.66-0.68	16	15.2±4.8	4.0±2.5	20.9±9.4	50.9±2.5	4.3±2.0	95.3±3.4^d
3^f	0.66	16	6.0	12.7	3.2	54.6	4.2	80.7^d
4	0.99	16	2.4	0	79.8	18.8	0	101.0
5	0.97	0.017	86.8	0	5.2	2.2	1.3	95.5
6	0.97	0.25	59.1	0	29.6	7.9	0	96.6
7	0.97	3	21.0	0	50.2	22.5	0	93.7
8	1.3	16	1.5	0	99.8	2.2	0	103.5
9^f	1.3	16	10.6	0	60.8	29.6	0	101.0

[a] The reaction ampoules were degassed, sealed and thermostated before mixing the materials, unless otherwise specified.

[b] Initial concentration of I $\doteq$ 0.15 M

[c] This is based on the starting mmole of the substrate.

[d] Traces of phenylacetaldehyde were identified by glpc-ms and glpc-ir.

[e] This is the mean result of three sets of experiments.

[f] The reaction ampoule was sealed, without degassing, and thermostated before mixing the materials.

A similar investigation of the reaction of alcohol II and aluminum hydride was thus conducted. The results are listed in Table VII. It appeared that the variation of the relative yield of the two defluorinated alcohols with the change of the mole ratio of the hydride to the alcohol followed a similar pattern as that for the corresponding reaction of I.

Undegassed reactions were studied briefly. Oxygen probably consumed the hydride reagent since alcohol III, whose yield increased with the amount of the reducing agent, was obtained in a smaller quantity under undegassed conditions (Reactions 2 and 3, 8 and 9, Table VI; Reactions 7 and 8, Table VII). This was accompanied by the elevation of the product yield of IV compared with similar runs under degassed condition.

The preponderance of alcohol IV at lower hydride-to-substrate ratios and of alcohol III at higher ratios was a trend shared by the reduction of styrene oxide (V) with aluminum hydride, as revealed by the results in Table VIII (p. 63).

Nevertheless, the composition of the defluorinated products from the reaction of the alcohol with aluminum deuteride was rather different from that obtained from the corresponding reduction of V. These results are shown in

Table VII

Reaction of 2-fluoro-1-phenylethanol (II) with various quantities of aluminum hydride in THF at 61°[a]

Reaction	Mole[b] AlH_3/II	Reaction Period, h	Product, Yield %[c]				Material Balance, %[c]
			$PhCOCH_3$	$PhCH(OH)CH_3$	$PhCH_2CH_2OH$	Unreacted Alcohol	
1	0.33	16	7.0	0	14.9	57.1	$\gtrsim$79.0[d]
2[e]	0.71	18	0	15.3±2.5	50.8±0.8	30.6±0.9	96.7±3.9
3	0.71	0.25	0	2.8	14.8	84.6	102.2
4	0.71	1	0	3.9	24.2	72.1	100.2
5	0.71	3	0	10.8	34.0	54.2	99.0
6	0.71	8	0	14.6	43.9	38.1	96.6
7	0.98[f]	16	0	77.2	13.3	5.6	96.1
8[g]	0.98[f]	16	7.9	20.9	47.0	13.7	$\gtrsim$89.5[d]
9	1.3	16	0	95.3	4.9	3.4	103.6

[a] The reaction ampoules were degassed, sealed and thermostated before mixing the materials, unless otherwise specified.

[b] Initial concentration of II = 0.15 M, unless otherwise specified.

[c] This is based on the starting mmole of the substrate.

[d] Traces of phenylacetaldehyde were identified by glpc-ms and glpc-ir.

[e] This is the mean result of three sets of experiments.

[f] Initial concentration of II = 0.13 M.

[g] The reaction ampoule was sealed, without degassing, and thermostated before mixing the materials.

Table VIII

Reaction of styrene oxide (V) with two different quantities of aluminum hydride in THF at 61°[a]

Reaction	Mole[b] AlH_3/V	Product, Yield %[c]		Unreacted Epoxide	Material Balance, %[c]
		$PhCH(OH)CH_3$	$PhCH_2CH_2OH$		
1	0.32	17.5	81.4	1.9	100.8
2	0.64	45.0	55.6	0	100.6

[a] The reaction ampoules were degassed, sealed and thermostated before mixing the materials. Reaction period was 16 h.

[b] Initial concentration of V = 0.15 M.

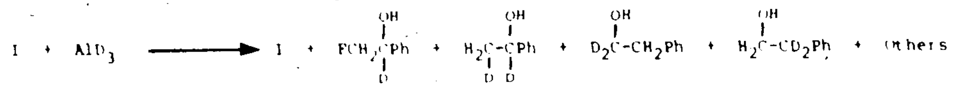
[c] This is based on the starting mmole of the substrate.

Table IX. Also included in this table are the results obtained from the reduction of I with the reagent. Figures 3A and 3B present the ^1H and ^2H nmr spectra of the product mixtures from the reaction of alcohol II with two different quantities of aluminum deuteride.

The effects of p-DNB and DCB on the reaction were also examined. It was found that there was little difference in the product compositions whether p-DNB was present or not. In the presence of DCB, the yields of the defluorinated alcohols were considerably less. Post-

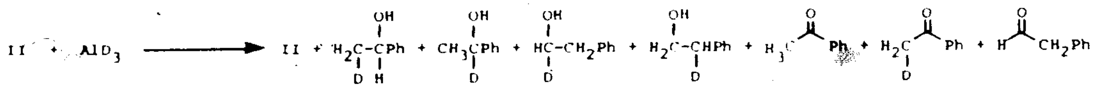
Table IX

Reactions of α-fluoroacetophenone (I), 2-fluoro-1-phenylethanol (II) and styrene oxide (V) with aluminum deuteride in THF at 61°^{a,b}



$$\mathrm{I} + \mathrm{AlD_3} \longrightarrow \mathrm{I} + \mathrm{FCH_2}\overset{\mathrm{OH}}{\underset{\mathrm{D}}{\mathrm{C}}}\mathrm{Ph} + \mathrm{H_2}\underset{\mathrm{D}}{\mathrm{C}}-\overset{\mathrm{OH}}{\underset{\mathrm{D}}{\mathrm{C}}}\mathrm{Ph} + \mathrm{D_2}\overset{\mathrm{OH}}{\mathrm{C}}-\mathrm{CH_2Ph} + \mathrm{H_2}\overset{\mathrm{OH}}{\mathrm{C}}-\mathrm{CD_2Ph} + \text{others}$$

	[I],M	Mole AlD$_3$/I	Reaction Period, h	Product composition, %^{c}					
(1)	0.071	1.8	3	0	0	95.1	3.4	1.5	0
(2)	0.14	0.63	3	10.1	19.7	27.3	38.8	4.1	d



$$\mathrm{II} + \mathrm{AlD_3} \longrightarrow \mathrm{II} + \mathrm{H_2}\underset{\mathrm{D}}{\mathrm{C}}-\overset{\mathrm{OH}}{\underset{\mathrm{H}}{\mathrm{C}}}\mathrm{Ph} + \mathrm{CH_3}\overset{\mathrm{OH}}{\underset{\mathrm{D}}{\mathrm{C}}}\mathrm{Ph} + \mathrm{H}\overset{\mathrm{OH}}{\underset{\mathrm{D}}{\mathrm{C}}}-\mathrm{CH_2Ph} + \mathrm{H_2}\overset{\mathrm{OH}}{\mathrm{C}}-\underset{\mathrm{D}}{\mathrm{C}}\mathrm{HPh} + \mathrm{H_3C}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Ph} + \mathrm{H_2}\underset{\mathrm{D}}{\mathrm{C}}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Ph} + \mathrm{H}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{CH_2Ph}$$

	[II],M	Mole AlD$_3$/II	Reaction Period, h	Product composition, %^{c}							
(3)	0.070	1.8	3	0	97.9	0	2.1	0	0	0	0
(4)	0.14	0.64	16	5.6	29.9	1.8	52.2	1.8	1.5^e	6.0^e	1.2^e

$$+ \mathrm{AlD_3} \longrightarrow \mathrm{H_2}\underset{\mathrm{D}}{\mathrm{C}}-\overset{\mathrm{OH}}{\underset{\mathrm{H}}{\mathrm{C}}}\mathrm{Ph} + \mathrm{H_2}\overset{\mathrm{OH}}{\mathrm{C}}-\underset{\mathrm{D}}{\mathrm{C}}\mathrm{HPh}$$

	[V],M	Mole AlD$_3$/V	Reaction Period, h	Product composition, %^{c}	
(5)	0.15	0.65	16	57.6	43.4

---

[a] The reaction ampoules were degassed, sealed and thermostated before mixing the materials. The reaction mixture was worked up by treating with H_2SO_4-H_2O.

[b] The structures of the products were elucidated from their ^1H and ^2H nmr spectra.

[c] This is based on a combination of the molar ratios from glpc analysis and ^1H and ^2H nmr integrations.

[d] Glpc analysis showed the presence of either phenylacetaldehyde or acetophenone or both. This was not detectable from nmr analyses.

[e] This was analyzed by a combination of nmr spectra, glpc, glpc-ms and glpc-ir.

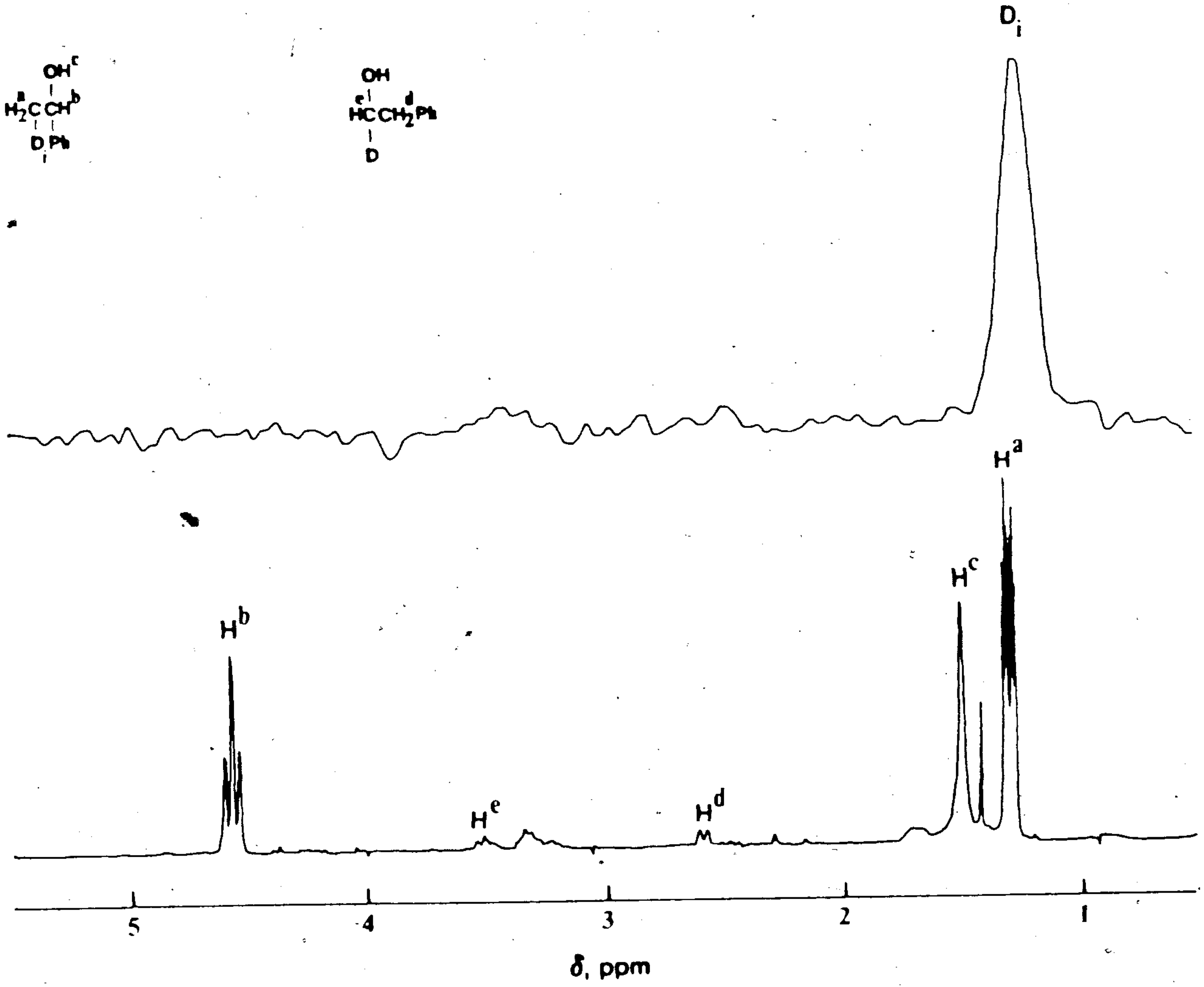


Figure 3A. 200 MHz ^{1}H (bottom) and ^{2}H NMR Spectra of the product mixture from the reaction of 2-fluoro-1-phenylethanol with excess aluminum deuteride in THF.

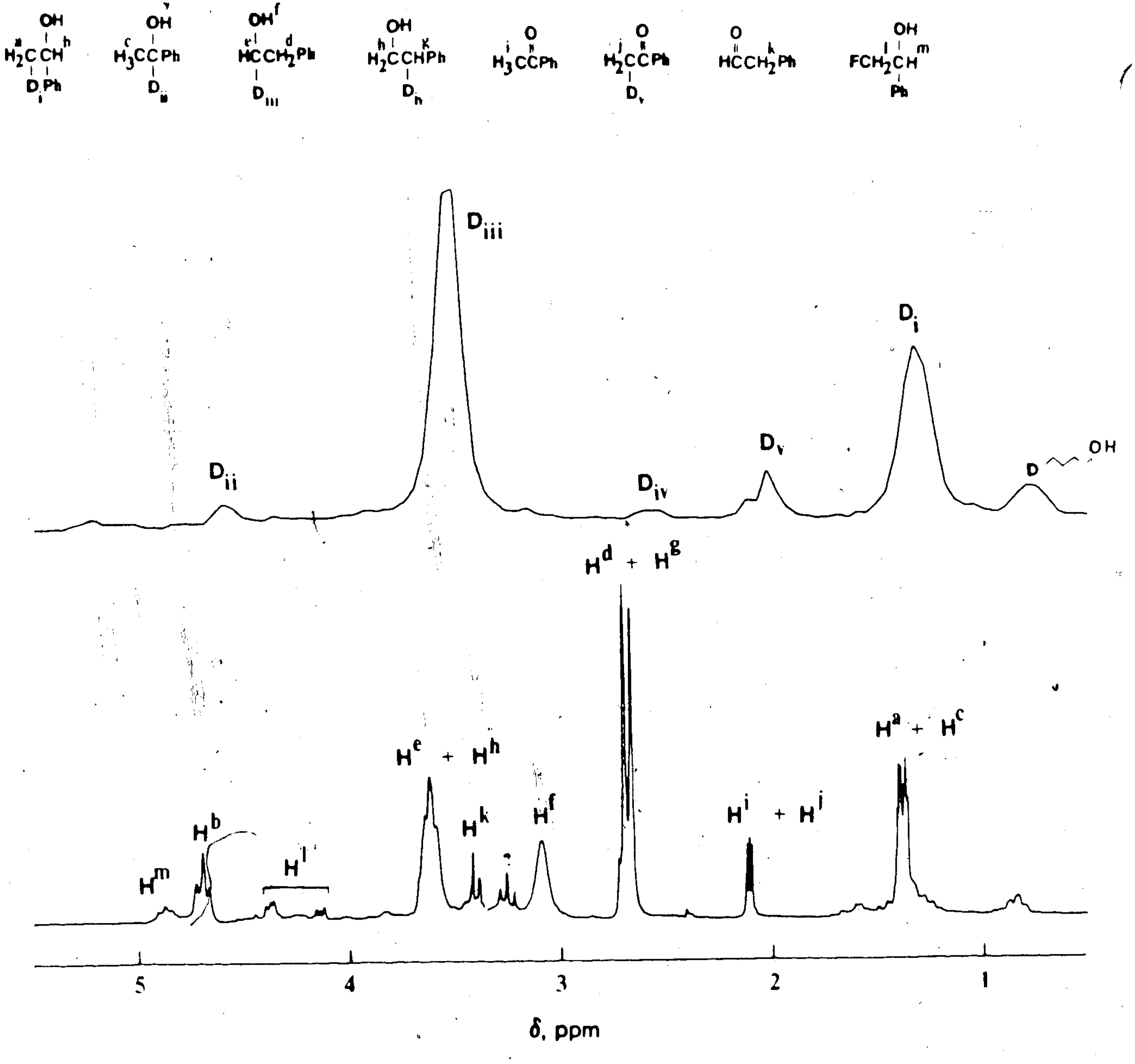


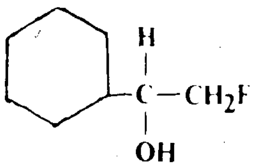
Figure 3B. 200 MHz ^1H (bottom) and ^2H NMR Spectra of the product mixture from the reaction of 2-fluoro-1-phenylethanol with limited amount of aluminum deuteride in THF.

treatment of reaction mixtures with cyclohexanone showed that no excess hydride was available for the reaction of I in the presence of DCB while excess reducing agent was associated with the reaction without the additive.

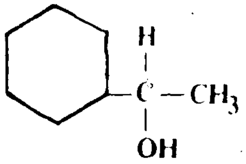
The possibility of isomerization between alcohols III and IV in the presence of aluminum hydride was tested (see Experimental). A synthetic mixture of these alcohols was found to be fixed in composition when subjected to the normal reaction conditions (degassed/61°/16 h).

II.3 The Reaction of Cyclohexyl Fluoromethyl Ketone (VI) with Lithium Aluminum Hydride

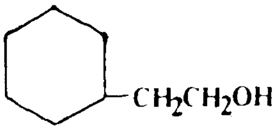
When the ketone VI was treated with lithium aluminum hydride in benzene, four products were obtained, viz, 1-cyclohexyl-2-fluoroethanol (VII), 1-cyclohexylethanol (VIII), 2-cyclohexylethanol (IX) and 1-cyclohexyl-1,2-epoxyethane (X). These products were also detected from the reaction in THF. Epoxide X was found to be destroyed during the acid work-up of the reaction in the latter



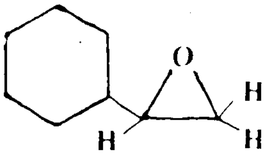
VII



VIII



IX



X

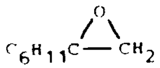
medium. This was in accord with two observations. First, when a reaction mixture was analyzed by glpc before the treatment with aqueous acid, a product whose retention time corresponded to X was detected. This product disappeared and replaced by two new ones when the mixture was subject to hydrolysis. Second, a synthetic sample of X was likewise shown to be labile to acid hydrolysis in solvent THF. The glpc retention times of the two hydrolysis products were the same as those of the new materials from the hydrolyzed reaction mixture. Since the epoxide did not undergo hydrolysis in benzene, the reaction mixture in THF was treated with an aliquot of benzene prior to the addition of aqueous acid. It was then found that the yield of X was the same as that determined from the corresponding unhydrolyzed reaction mixture.

In either solvent, increasing the ratio of hydride/substrate facilitated the production of VIII, see Table X. At the maximum ratio employed, the combined yield of the other products was less than 5%. The variation of the product composition with time was studied. It was observed that the fluoroketone was reduced readily to the corresponding fluoroalcohol whose yield declined subsequently. Parallel to this was the gradual accumulation of its defluorinated analog VIII.

Table X

Reactions of cyclohexyl fluoromethyl ketone (VI) and
1-cyclohexyl-2-fluoroethanol (VII) with lithium aluminum hydride (LAH) at 61°^{a}

(A) Reaction in Benzene^{b}

Reaction No	Substrate^{c}	Mole LAH/ Substrate	Reaction Period, h	Product, Yield %^{d}					Material Balance, %^{d}
				$C_6H_{11}COCH_2F$	$C_6H_{11}CH(OH)CH_2F$	$C_6H_{11}CH(OH)CH_3$	$C_6H_{11}CH_2CH_2OH$	 $C_6H_{11}\overset{O}{C}$—CH_2	
1	VI	0.38	16	2.9	60.2	27.8	traces	1.4	≥92.3
2	VI	0.76	17	0	18.7	76.3	0.3	1.3	97.0
3	VI	0.97	0.017	94.7	0.7	0	0	0	95[illegible]
4	VI	0.97	0.15	0	94.3	2.3	0	0.8	97[illegible]
5	VI	0.97	1	0	52.5	44.3	traces	0	≥[illegible]8
6	VI	0.97	3	0	22.1	69.7	traces	0	≥[illegible]8
7	VI	0.97	8	0	11.0	78.5	0.2	0	[illegible].8
8	VI	1.0	16	0	6.7	89.9	0.3	0	96.9
9	VI	1.6	16	0	4.5	89.9	0.3	0	94.7
10	VII	0.78	17	-	14.9	74.6	0.6	0	90.1
11	VII	1.1	17	-	8.7	91.3	traces	0	≥100.0

continued.....

Table X (continued):

(B) Reaction in THF

Reaction No	Substrate	Mole LAH/ Substrate	Reaction Period, h	Product, Yield %[d]					Material Balance, %[d]
				$FCH_2COC_6H_{11}$	$FCH_2CH(OH)C_6H_{11}$	$CH_3CH(OH)C_6H_{11}$	$HOCH_2CH_2C_6H_{11}$	 C_6H_{11}	
1	VI, 0.15	0.35	16	21.2	69.0	0.2	0	1.9	92.3
2	VI, 0.15	0.60	17	0	72.7	33.0	0.6	1.7	105.7
3	VI, 0.15	0.96	17	0	3.1	87.1	1.5	traces	≳91.7
4	VI, 0.10	1.6	0.017	0	104.9	3.4	0	0	108.4
5	VI, 0.10	1.6	0.25	0	87.9	10.1	0	0.2	98.2
6	VI, 0.10	1.6	1	0	50.8	38.2	0	traces	≳89.0
7	VI, 0.10	1.6	3	0	2.4	97.7	0	0.4	100.5
8	VII, 0.15	0.58	17	-	75.7	21.2	0	2.6	99.5
9	VII, 0.19	0.87	16	0	19.4	72.6	traces	tra[illegible]	≳92.0

---

[a] The reaction ampoules were degassed, sealed and thermostated before mixing the materials.

[b] Slurry of LAH in benzene was employed without stirring.

[c] The initial concentration of the substrate was 0.20 M.

[d] This is based on the starting mmole of the substrate.

When the synthetic compound VII was allowed to react with the hydride reagent in benzene or in THF, the same series of defluorinated products was found. The product composition versus hydride-to-substrate ratio followed a similar trend as that of the fluoroketone reaction.

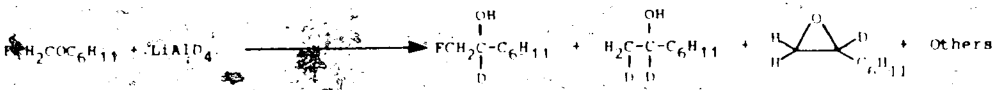
Each of the fluoroketone and the fluoroalcohol was mixed with lithium hydride in THF. Since both compounds were found to be inert towards lithium hydride which is present in commercial LAH, the reagent was used in benzene without purification.

Reactions of VII, VIII and epoxide X were carried out with LAD, since it was conceivable that X was a possible intermediate from which the defluorinated alcohols arose. The results are listed in Table XI. Figure 4 shows the ^1H and ^2H nmr spectra of the product mixture from the reaction of alcohol VIII with LAD in THF.

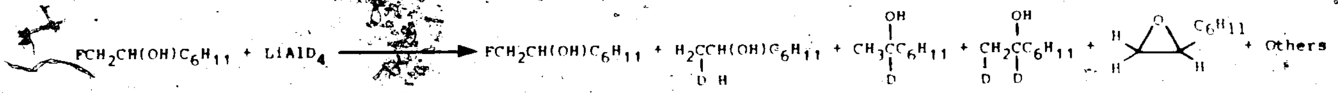
The effects of AIBN, m-DNB and DCB on the reaction in benzene were studied. The results are presented in Table XII. It appeared that AIBN only affect the yield of each product slightly. On the other hand, m-DNB and DCB suppressed the formation of the defluorinated alcohols. More than 50% of the added quantity of DCB was recovered upon the reaction (Reactions 4 and 8). Less excess hydride was associated with the reaction mixture containing m-DNB compared with the one without the

Table XI

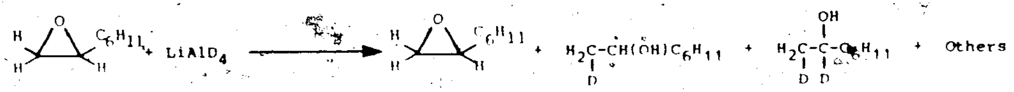
Reactions of cyclohexyl fluoromethyl ketone (VI), 1-cyclohexyl-2-fluoroethanol (VII) and 1-cyclohexyl-1,2-epoxyethane (X) with lithium aluminum deuteride (LAD) at 61°[a-c]



	[VI],M	Mole LAD/VI	Reaction Period, h	Reaction Medium	Product composition, %[d]			
(1)	0.21	0.68	20	Benzene	33.6	66.4	(traces)[e]	0
(2)	0.15	0.74	16	THF	11.4	82.5	6.1	f



	[VII],M	Mole LAD/VII	Reaction Period, h	Reaction Medium	Product composition, %[d]					
(3)	0.20	0.72	3	Benzene	40.3	52.2	0	5.7	1.6	f
(4)	0.15	0.76	16	THF	10.1	82.3	2.1	0[g]	4.7	f



	[X],M	Mole LAD/X	Reaction Period, h	Reaction Medium	Product Composition, %[d]			
(5)	0.13	1.1	22	Benzene	0	84.6	15.4	f
(6)	0.15	0.50	16	THF	0	98.4	0	f

---

[a] Slurry of LAD was used in benzene without stirring. For the reaction in [illegible], solution of the deuteride reagent was employed.

[b] The reaction ampoules were degassed, sealed and thermostated before mixing the materials. Each reaction mixture was worked up by treating with H$_2$SO$_4$-H$_2$O.

[c] The structures of the products were elucidated from their ^{1}H and ^{2}H spectra.

[d] This is based on a combination of the molar ratios from glpc analysis and ^{1}H and ^{2}H integrations.

[e] By glpc analysis, signal corresponding to X was detected.

[f] Traces of a product whose glpc retention time corresponded to that of 2-cyclohexylethanol (IX) were detected. In reaction (3), the yield of this product was 0.2%.

[g] Dideuterated derivative(s) of 1-cyclohexylethanol was excluded form glpc-ms analysis.

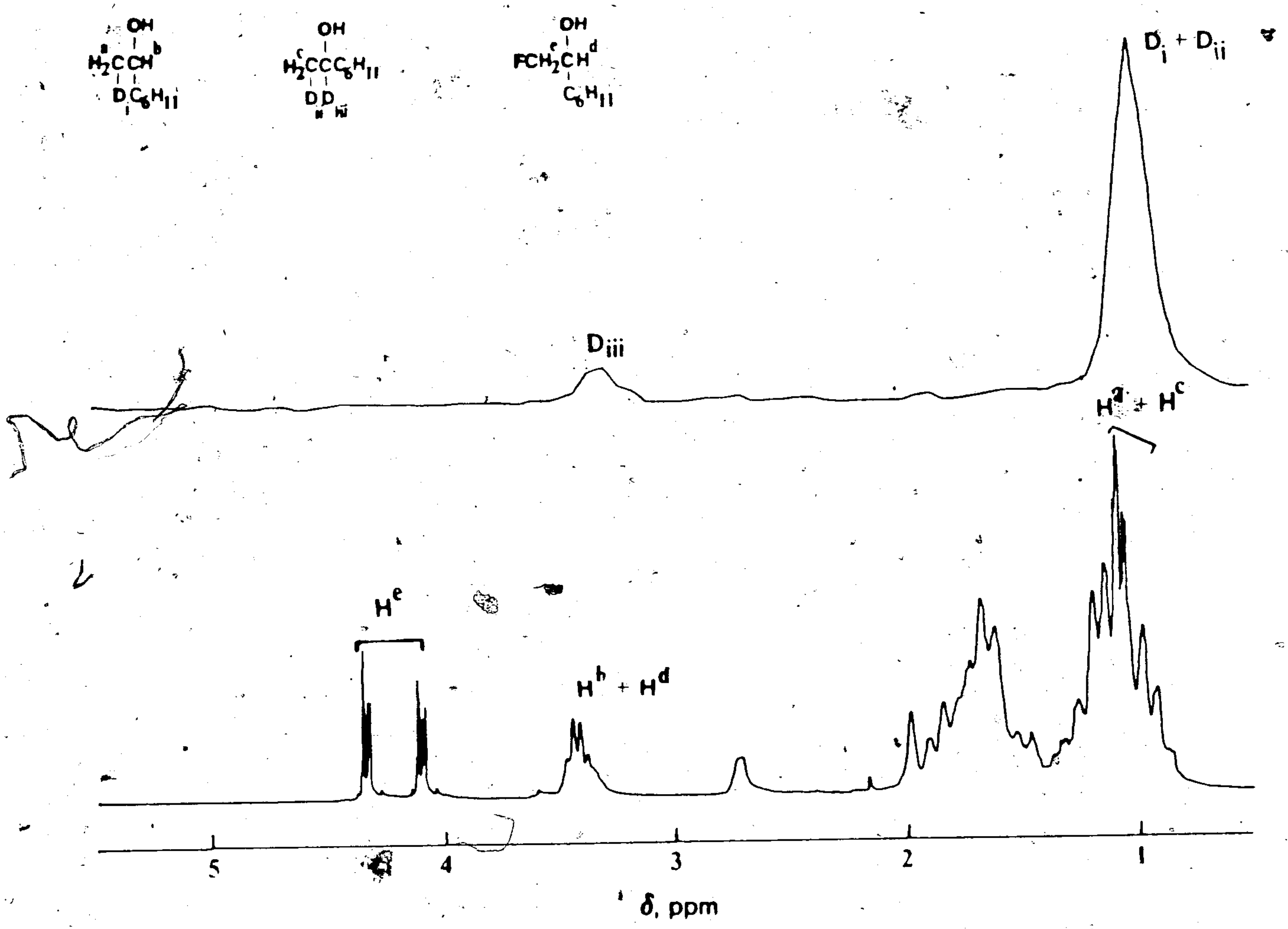


Figure 4. 200 MHz ^{1}H (bottom) and ^{2}H NMR Spectra of the product mixture from the reaction of 1-cyclohexyl-2-fluoroethanol with LAD in THF.

Table XII

Reactions of cyclohexyl fluoromethyl ketone (VI) and 1-cyclohexyl-2-fluoroethanol (VII) with lithium aluminum hydride (LAH) in benzene at 61° in the presence of additives[a,b]

Reaction	Substrate[c]	Mole LAH/ substrate	Additive, %[d]	Product, yield %[d]					Material Balance, %[d]
				$C_6H_{11}COCH_2F$	$C_6H_{11}CH(OH)CH_2F$	$C_6H_{11}CH(OH)CH_3$	$C_6H_{11}CH_2CH_2OH$	$C_6H_{11}\overset{O}{C{-}CH_2}$	
1	VI	0.76	-	[illegible]	18.7	76.3	0.3	1.3	97.0
2	VI	0.76	AIBN,[e] 7.4	[illegible]	21.6	81.4	0.3	traces	≥103.3
3	VI	0.76	m-DNB,[e] 6.5	~0	91.8	5.4	0	4.4	101.6
4	VI	0.76	DCB,[e,f] 5.6	0	93.6	6.4	0	4.8	104.8
5	VII	0.78	-	-	14.9	74.6	0.6	0	90.1
6	VII	0.79	AIBN,[e] 6.5	-	11.6	80.3	0.3	0	92.2
7	VII	0.79	m-DNB,[e] 6.6	-	80.8	7.0	0	2.4	90.2
8	V[illegible]	0.79	DCB,[e,g] 5.7	-	90.8	3.8	0	3.2	97.8
9[h]	VI	1.0	Nil[i]	0	52.9	43.2	0	0.2	96.3
10[h]	VI	1.1	m-DNB,[e,j] 5.4	0	96.9	1.7	0	1.7	100.3

---

[a] Slurry of LAH was used for each reaction without stirring.

[b] The reaction ampoules were degassed, sealed and thermostated before the materials were mixed. The reaction period was 17 h, unless otherwise specified.

[c] Initial concentration of the substrate = 0.20 M.

[d] This is based on the starting mmole of the substrate.

[e] AIBN = α,α'-azobisisobutyronitrile; m-DNB = 1,3-dinitrobenzene; DCB = 1,4-dicyanobenzene.

[f] 3.7% (relative to starting mmole of the substrate) DCB was recovered.

[g] 3.0% (relative to starting mmole of the substrate) DCB was recovered.

[h] The reaction period was 1 h.

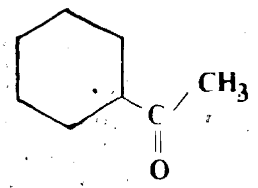
[i] An identical experiment was carried out and from which the reaction mixture was treated with 70% (relative to starting mmole of substrate) cyclohexanone for 1 h, only traces of cyclohexanone remained.

[j] An identical experiment was carried out and from which the reaction mixture was treated with 70% (relative to starting mmole of substrate) cyclohexanone for 1 h, mole cyclohexanone/cyclohexanol = 0.66.

additive (Reactions 9 and 10). In THF, it was found that the formation of the dehalogenated alcohols was also suppressed but not as notable as in benzene.

II.4 The Reaction of Cyclohexyl Fluoromethyl Ketone (VI) with Aluminum Hydride in Tetrahydrofuran

The products of the reaction of ketone VI with AlH_3 resembled those obtained from its LAH reaction except that an additional product, cyclohexyl methyl ketone (XI), was detected. Moreover, the epoxide X was produced in a significant amount. Increasing the proportion of the hydride reagent favored the yield of VIII. Table XIII lists the results for the reactions of VI and VII. A study of the variation of product composition with time at a hydride-to-substrate ratio of about 0.6 reflected the following:



XI

(a) The ketone substrate was converted to the fluoroalcohol in more that 80% during the first minute of

Table XIII

Reactions of cyclohexyl fluoromethyl ketone (VI) and 1-cyclohexyl-2-fluoroethanol (VII) with aluminum hydride in THF at 61°[a]

Reaction No.	Substrate[b]	Mole AlH_3/ substrate	Reaction Period, h	Product Yield, %[c]						Material Balance, %[c]
				$C_6H_{11}COCH_2F$	$C_6H_{11}CH(OH)CH_2F$	$C_6H_{11}COCH_3$	$C_6H_{11}CH(OH)CH_3$	$C_6H_{11}CH_2CH_2OH$	$C_6H_{11}C\overset{O}{-}CH_2$	
1	VI	0.70	16	0	6.4	1.5	57.7	8.6	27.4	101.6
2	VI	0.64	0.017	[illegible]	[illegible]	0	4.9	0.4	2.3	98.1
3	VI	0.64	0.25	[illegible]	[illegible]	0.4	19.5	1.2	16.4	102.1
4	VI	0.64	1	0.9	[illegible]	1.6	34.3	3.0	32.0	102.9
5	VI	0.64	3	0	10.0	6.7	32.8	4.8	43.1	97.4
6	VI	0.64	8	0	4.8	10.2	36.6	9.7	39.3	100.6
7	VI	1.0	16	0	4.9	0.9	82.5	4.6	2.7	95.6
8	VI	1.6	16	0	2.6	0	89.9	1.4	6.3	100.2
9[d]	VII	0.70	16	–	[illegible]	2.6±0.8	61.2±1.6	8.6±1.3	19.9±3.5	95.8±2.4
10	X[e]	0.38	3	–	[illegible]	0	43.0	2.9	45.4	91.3

---

[a] The reaction ampoules were degassed, sealed and thermostated before mixing [illegible] materials.

[b] Initial concentration of the substrate = 0.15 M in all cases.

[c] This is based on the starting mmole of the substrate.

[d] This is the mean result of two identical experiments.

[e] X = 1-cyclohexyl-1,2-epoxyethane.

the reaction. Thereafter, the yield of the alcohol decreased with time.

(b) The defluorinated ketone, XI, the epoxide X, and the defluorinated alcohols were formed simultaneously; X and VII were the major products.

(c) Alcohol IX was produced as high as 10%, unlike the reaction with LAH which afforded a barely detectable quantity.

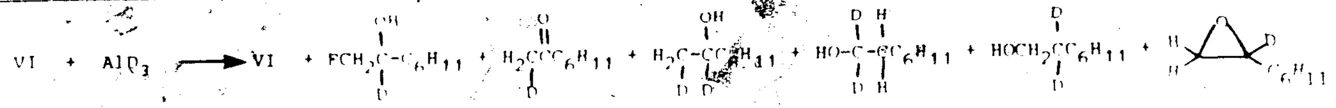
It appeared that the fluoroalcohol was dehalogenated in a similar pattern since the product composition resembled closely to that from the reaction of the fluoroketone with comparable amount of aluminum hydride (Reactions 1 and 9).

It was suspected that ketone XI might come directly from epoxide X during the course of the reaction. Control experiment with the epoxide in the presence of a limited quantity of aluminum hydride suggested that only alcohols VIII and IX were formed as a consequence of epoxide opening (Reaction 10, Table XIII). Another control experiment tested the possibility of isomerization between VIII and IX with excess hydride reagent. Glpc analysis of the mixture precluded interconversion of the defluorinated isomeric alcohols with AlH_3.

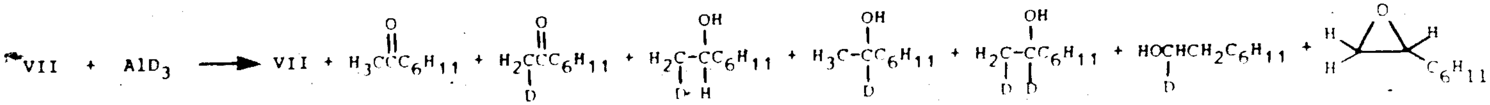
As with the previous tracer experiments, the examination of deuterium incorporation into the products of the reaction with the deuteride reagent is pivotal in the mechanistic studies of the formation of defluorinated compounds. The aluminum deuteride reaction was carried out for substrates VI, VII and epoxide X, and the results are presented in Table XIV. Figure 5 depicts the ^1H and ^2H nmr spectra of the product mixture resulted from the AlD_3 reaction with VI.

Table XIV

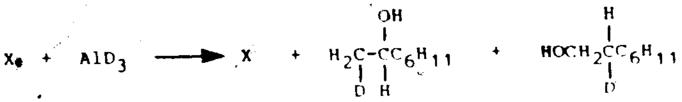
Reactions of cyclohexyl fluoromethyl ketone (VI), 1-cyclohexyl-2-fluoroethanol (VII) and 1-cyclohexyl-1,2-epoxyethane (X) with aluminum deuteride in THF at 61°[a,b]



	[VI],M	Mole AlD$_3$/VI	Product composition, %[c,d]						
(1)	0.18	0.56	0.8	2.9	8.6	32.2	6.6	1.5	45.6



	[VII],M	Mole AlD$_3$/VII	Product composition, %[c,d]							
(2)	0.19	0.58	2.8	2.2	5.3	26.2	10.0	6.2	7.9	39.4



	[X],M	Mole AlD$_3$/X	Product Composition, %[d]		
(3)	0.15	0.49	1.6	95.5	2.9

---

[a] The reaction ampoules were degassed, sealed and thermostated before the materials were mixed. The reaction period was 16 h and each reaction mixture was worked up by treating with H_2SO_4-H_2O.

[b] The structures of the products were elucidated from ^1H and ^2H NMR spectra.

[c] Glpc-ms analysis was carried out to assist structural elucidation and to confirm NMR analyses.

[d] Percent composition was determined by a combination of molar ratios from glpc and ^1H and ^2H NMR integrations.

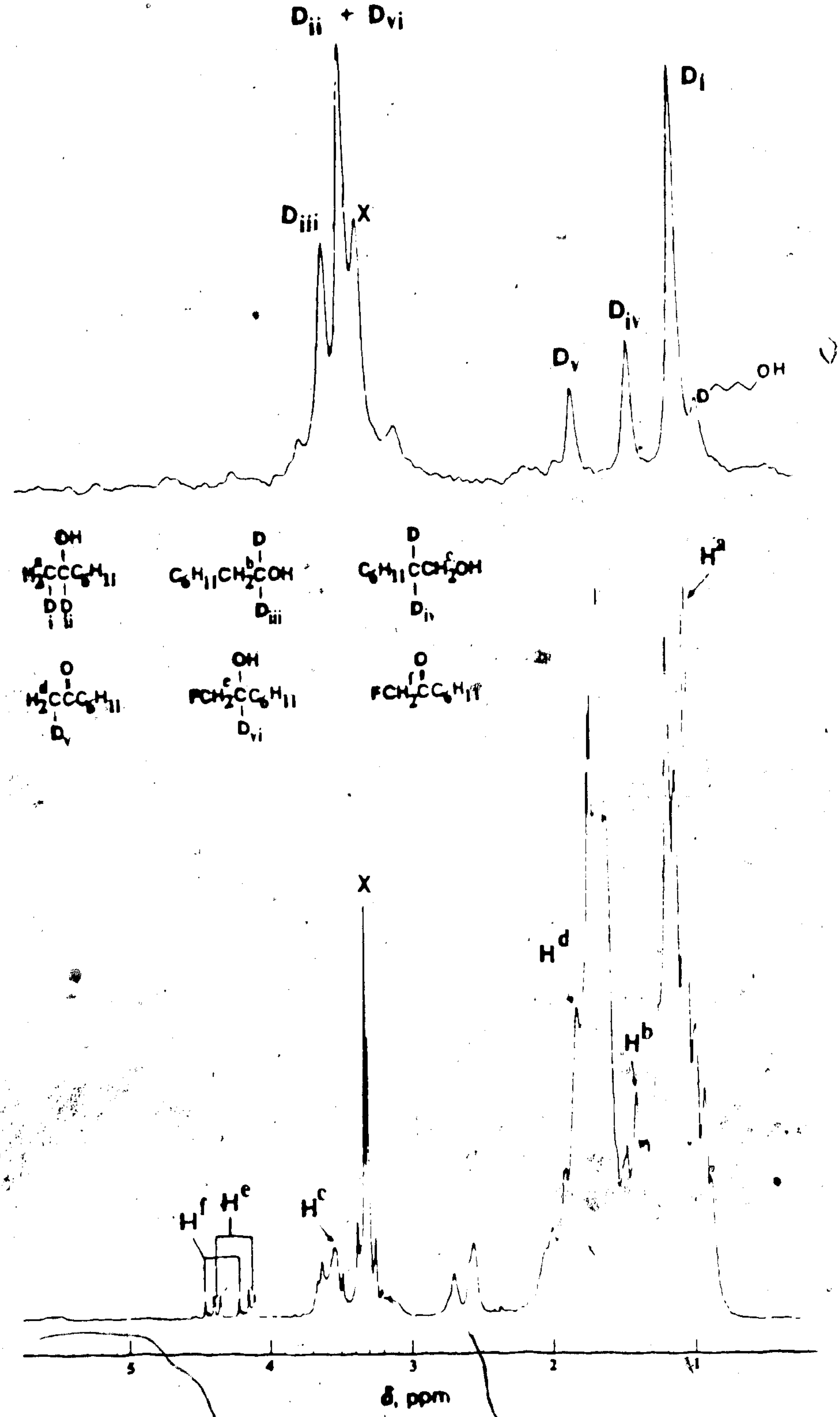


Figure 5. 200 MHz ¹H (bottom) and ²H NMR Spectra of the product mixture from the reaction of cyclohexyl fluoromethyl ketone with aluminum deuteride in THF (X corresponds to the product(s) derived from acid hydrolysis of 1-cyclohexyl-1,2-epoxyethane).

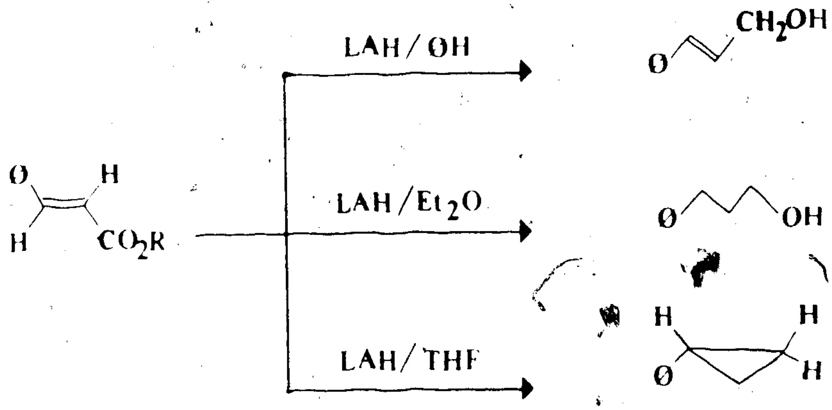
DISCUSSION

α-Fluoroacetophenone (I) had been reported[129] to react with LAH at 0° in absolute ether to yield 2-fluoro-1-phenylethanol (III) as the sole product only if the mixture was decomposed immediately upon the addition of the ketone to the hydride. At refluxing temperature of diethyl ether, halogen-free products were obtained. These products were not identified in the report and no further attempt was shown to study the reaction.

In the present study, the conversion of α-fluoroketones I and VI to their corresponding fluoroalkoxides by lithium aluminum hydride prior to dehalogenation is in agreement with the results of previous investigators for the LAH reduction of α-bromoacetophenones,[130,131] and several chlorocarboxylic acids.[53] The reaction of I and VII with aluminum hydride behaves [illegible]. This process of ketone to alkoxide, effected by either reagent, is more rapid than the defluorination of the alkoxide itself. Nevertheless, the latter reaction is still an efficient process even with aluminum hydride, despite the sluggishness shown by this reagent during its hydrogenolysis of alkyl halides.[13]

III.1 The Reduction of α-Fluoroketones with LAH

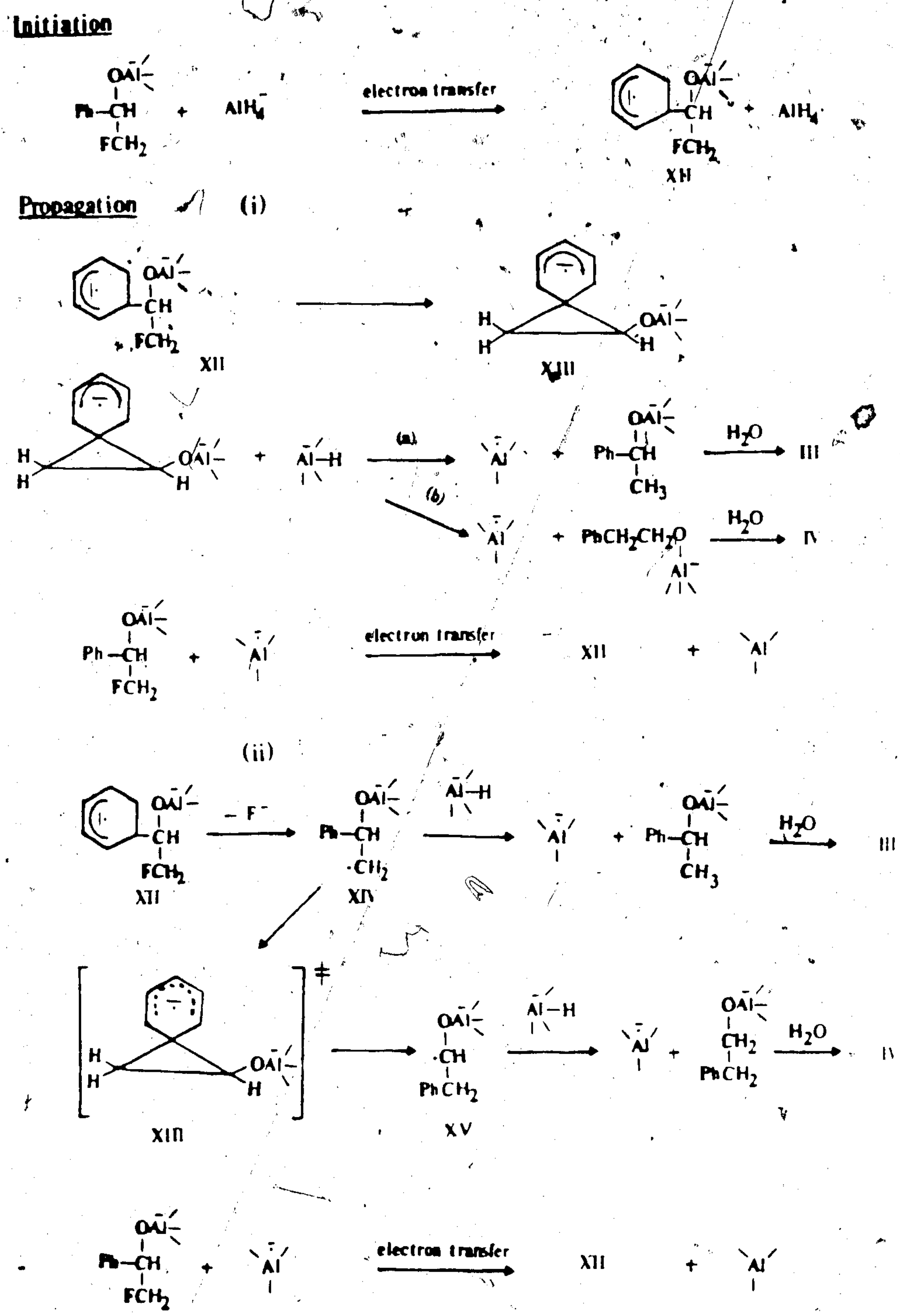
Solvent benzene has been employed for LAH reduction by previous workers. A good yield of 3-phenyl-1-propanol was reported for the reduction of methyl hydrocinnamate.[132] Methyl cinnamate was found to be reduced to cinnamyl alcohol, whereas concomitant hydrogenation of the carbon-carbon double bond was observed for the corresponding reaction in diethyl ether.[16a] Snyder[16a] attributed the results to the Lewis base character of diethyl ether which coordinates aluminum and facilitates intramolecular hydride transfer from the metal center to the olefin moiety. With an even stronger Lewis base THF, hydride transfer to the carbon-carbon double bond is followed by the formation of cyclopropane[133] from the cinnamate system.



Differences in the outcome of the reaction in benzene and in THF were noted during the course of the present study. It appeared that the rearranged alcohol, 2-phenylethanol (IV), was produced in a significant amount from the reaction of I or II in benzene, but only in traces in the other solvent. This observation was not extended to the reaction of the cyclohexyl-substituted substrates VI and VII, in which there was little difference in product composition whether the reactio[illegible]s carried out heterogeneously in benzene or homogeneo[illegible] in THF. The response of the reaction to the presence of common radical inhibitors appeared to be rather different in neither reaction medium. For the phenyl-substituted reactants I and II, defluorination was inhibited in benzene which contained a small amount of dinitrobenzene (DNB) or *p*-dicyanobenzene (DCB). The suppression was less extensive in THF. Yet, DCB was all consumed by the hydride reagent while at least 60% still remained from the reaction in benzene. The change in the quantity of the additive *m*- or *p*-dinitrobenzene was not determined. However, the works of Brown and coworkers[134] revealed the uptake of 5 molar equivs of hydride for the LAH reduction of nitrobenzene in THF. Hence 10-15% of LAH could be consumed in the presence of 4-6% DNB. The action of DNB on the present reaction resembled that of DCB in either solvent. The reduction of I to II was not influenced by these additives since LAH reacts more readily with the carbonyl function than with the nitro and the cyano groups. For the non-aromatic substrates VI and VII, dehalogenation was similarly affected by DCB or DNB.

Oxygen is another compound that consumes LAH, but only in THF. That less hydride was available for the undegassed reactions compared with the degassed ones was established by the lower reactivity of the remaining hydride with cyclohexanone. Higuchi[135] noticed that molecular oxygen reacted rather rapidly with LAH in solution since the effective hydride concentration in THF solution was found to be decreased to less than 20% five minutes after dry oxygen was bubbled through the solution.

The decrease in defluorinated products for the reaction in benzene, in the presence of a radical inhibitor, has prompted a comparison with the reactions of α-fluoroacetophenone with organotin hydrides.[95,128] The reaction with triphenyltin hydride was found to be very slow if uninitiated. In the presence of m-DNB (4%), the reaction was even slower. The introduction of AIBN (4%), however, catalyzed the dehalogenation with triphenyltin hydride, yielding 87% acetophenone. The LAH reaction of the same substrate was not affected by AIBN, but dehalogenation was inhibited by DNB and DCB. If the suppression by DNB is due to the consumption of the additive, then the effective amount of LAH could have been decreased by 10-15%[134] and so could have been the combined yield of the defluorinated alcohol. Nevertheless, it was found experimentally that decreasing the quantity of LAH by 20% in the absence of the additive decreased the combined yield of III and IV by about 20% (Reactions 3 and 4, Table I), while adding 4% m-DNB (i.e. the amount of LAH could have been decreased by a maximum of 10%) depreciated the combined yield from over 90% to less than 4% (Reactions 1 and 2, Table V). Consequently, it appears that m-DNB inhibits a radical reaction. Since inhibition is effective even in the presence of about 4% inhibitor, a radical propagation chain is likely to be operative in the defluorination of the aromatic substrates in benzene. The radical mechanism should involve the alkoxide derivative of II since the reaction of fluoroketone I begins with its rapid conversion to the corresponding fluoroalkoxide and this process is not inhibited. Moreover, the mechanism must account for the rearrangement process during the course of the reaction. In view of the current belief[60,62,64,108-116] that an electron transfer process is associated with the radical reactions involving LAH, the following is proposed:


Initiation
Ph–CH
FCH2
AlH4⁻
electron transfer
AlH4·
XII
Propagation
(i)
XII
XIII
Al–H
(a)
(b)
Ph–CH
CH3
H2O
III
PhCH2CH2O
IV
electron transfer
XII
(ii)
− F⁻
XII
XIV
H2O
III
XIII
XV
PhCH2
H2O
IV
V
electron transfer
XII

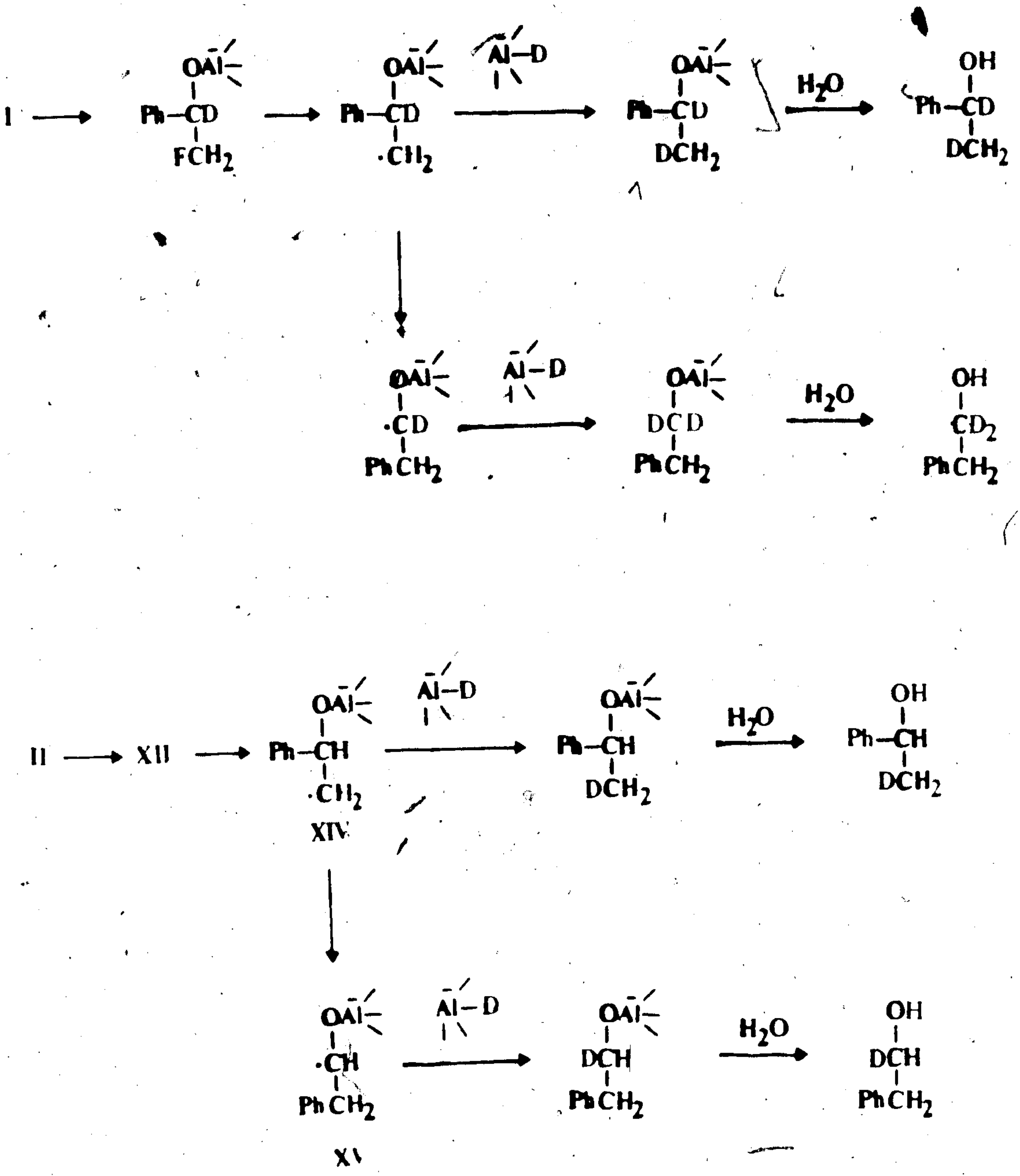
Scheme IX

Depending on the function of XIII, two possible propagation chains can be considered. As an intermediate (path (i)), XIII may abstract a hydrogen atom from an aluminohydride anion at either carbon leading upon hydrolysis, to the defluorinated alcohol III (<u>via</u> (a)) or IV (<u>via</u> (b)). For this process, the ratio of products III to IV would be independent of the relative amount of LAH to the substrate. On the other hand, XIII may be a transition state leading to the rearranged radical XV. Expulsion of fluoride ion from XII would lead to radical XIV which either abstracts a hydrogen atom from an aluminohydride ion to yield III on hydrolysis, or competitively rearranges to the more stable radical XV <u>via</u> the transition state XIII. The radical XV yields product IV upon hydrogen abstraction from an aluminohydride anion and hydrolysis. Since hydrogen abstraction of XIV is in competition with its rearrangement, increasing the concentration of hydride would favor the formation of III over that of IV. The data in Table I are in agreement with this prediction. Increasing the effective concentration of LAH by dissolving it in THF markedly enhances the bimolecular hydrogen atom transfer of XIV such that product III is formed almost exclusively. Similarly, stirring the heterogeneous medium during the course of the reaction in benzene promotes the product ratio III/IV.

Scheme IX is also consistent with the products obtained from the LAD reaction of fluoroketone I and fluoroalcohol II. Starting with the fluoroalcohol, the transfer of deuterium to XIV and XV respectively leads eventually to the deuterated alcohol products detected experimentally (see Scheme X). Likewise, the positions of deuteration of the defluorinated alcohols are predicted by Scheme IX for the LAD reaction of substrate I.

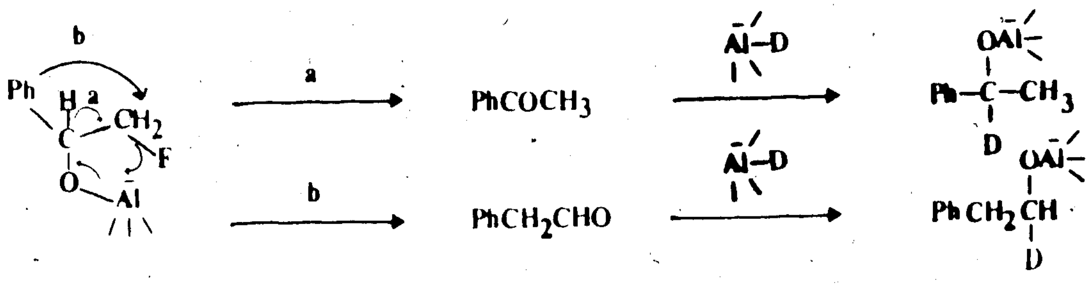
The formation of the rearranged alcohol IV had been observed for the reduction of α-fluoroacetophenone (I) with aluminum isopropoxide.[136] This observation was rationalized as involving an epoxide intermediate. However, when styrene oxide was allowed to react with LAD under the reaction conditions for the reduction of I, the deuteration of the primary alcohol product occurred at C-2. This finding is inconsistent with the position of deuteration of the rearranged defluorinated alcohol, IV, produced from the LAD reaction of II. Thus the intermediacy of an epoxide during the course of defluorination is excluded.

A minor ionic pathway probably occurs to give 1-phenylethanol-1-d from the LAD reaction of II. This product most likely results from the reduction of



Scheme X

acetophenone formed from a hydride shift of the fluoroalkoxide (see Scheme XI). Similarly, a phenyl shift of the latter furnishes phenylacetaldehyde. Both



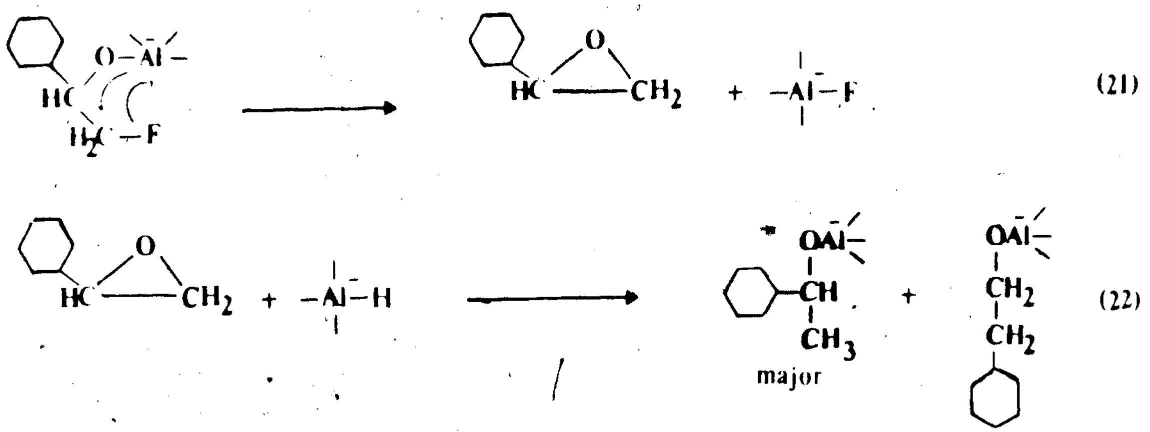
Scheme XI

acetophenone and phenylacetaldehyde were detected from the reaction in the presence of an inhibitor. The ionic pathway is not affected under these conditions.

The results for the reaction in THF agree with the competition of hydrogen atom abstraction of radical XIV and its rearrangement to XV via the transition state XIII, as depicted in Scheme IX. Since the effective concentration of the hydride is higher in THF, hydrogen atom abstraction dominates. The proposed mechanism in Scheme IX could be equally applicable to the reduction of I and II in THF. However, the radical inhibition of defluorination is not as remarkable as in benzene. As mentioned before, DNB and DCB are being consumed by LAH and probably very rapidly. Consequently, the inhibitory effect is annulled and at the same time, the supply of hydride is lowered. The introduction of DNB and DCB into the reaction mixture in THF, therefore, is not effective in testing the action of inhibitors on the defluorination.

Apparently, an analogous scheme including electron transfer process cannot be constructed for the dehalogenation of aliphatic substrates VI and VII. One indication is the formation of the rearranged alcohol IX only in traces. In benzene, defluorination of the cyclohexyl—substituted substrates appears to be suppressed by DCB and m-DNB. The test for excess hydride with cyclohexanone on reaction mixtures revealed that there was less available hydride associated with the reaction mixture containing m-DNB than the one without the additive. This indicates the consumption of m-DNB during the reaction.

Analogous to the ionic pathway for the dehalogenation of the aromatic substrates (i.e. Scheme XI), VI and VII may be defluorinated _via_ hydride and/or alkyl shift(s). One evidence of hydride shift is the yield of 1-cyclohexylethanol-1-d from the LAD reaction of the fluoroalcohol VII in THF. Yet rearrangement probably represents a minor route for the hydrogenolysis of C-F bond. Although an epoxide is dismissed as an intermediate in the defluorination of II, the detection of epoxide X from the reduction of VII suggests an alternate pathway for the dehalogenation of this substrate (see Scheme XII).



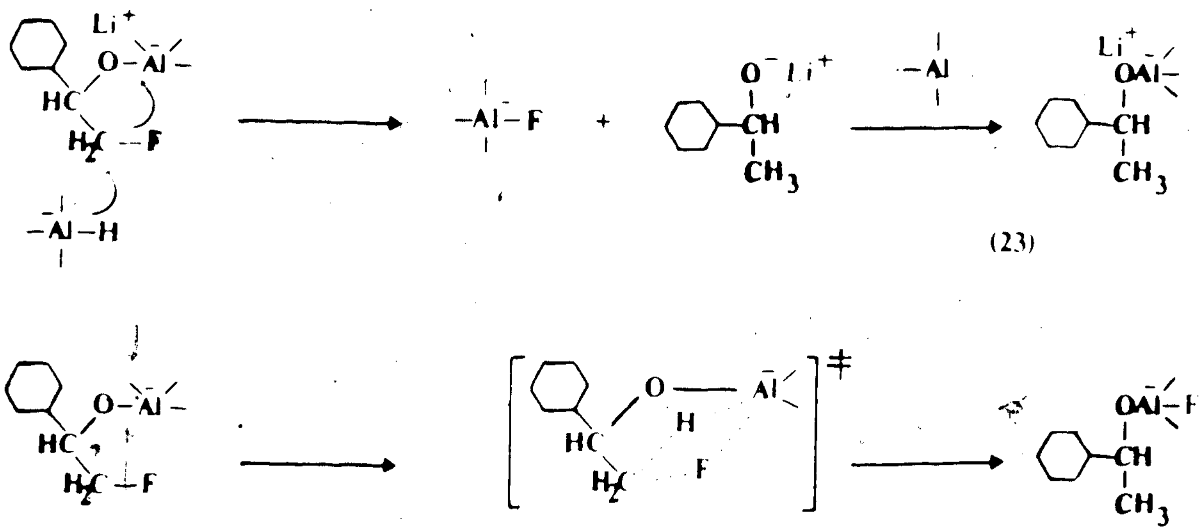
Scheme XII

The LAD reaction of synthetic 1-cyclohexyl-1,2-epoxyethane was found to give mainly the secondary alcohol in either THF or benzene. This observation is consistent with nucleophilic attack of a hydride species at the less highly substituted carbon. The defluorination of VI and VII resembles the reduction of epoxide X in that the secondary defluorinated alcohol (Compound VIII) is produced almost exclusively. That 1-cyclohexylethanol-1-d is the common product of the LAD reduction of epoxide X and of reactant VII is consistent with the intermediacy of an epoxide for the dehalogenation of VII.

Epoxide intermediacy has been invoked for the LAH dehalogenation of certain α-bromoketones.[38,130] The departure of bromide ion was taken for granted. In the present case, it is unlikely that the poor leaving group fluoride ion departs in the same manner. Displacement of fluoride ion from saturated carbon is rare.[105,137] Nevertheless, as depicted in Equation (21), the concerted process involving the formation of aluminum-fluorine bond and the breaking of carbon-fluorine bond may explain the ease of dehalogenation. Greater reactivity of C-F bond in fluorochloromethanes has been observed in the Friedel-Crafts reaction catalyzed by the halides of boron, aluminum and iron (III) and the reactivity order is R-F > R-Cl > R-Br > R-I.[138] Paleta[139] ascribed the higher reactivity of alkyl fluoride in the presence of aluminum halide catalysts to the greater difference in the bond dissociation energies between Al-F and C-F, which, therefore, represents higher energy gain than those with the bonds of chlorine and bromine.[140] It is likely that similar argument can be applicable to the defluorination of the α-fluoroalkoxide derivatives of AlH_4^- in an ionic pathway.

The presence of other organic functional group(s) in a fluoro compound has been shown to be crucial in the defluorination of the compound by LAH. So far, there has been no report on the hydrogenolysis of C-F bond of alkyl fluorides which contain no other functionality. Aryl fluorides have been demonstrated to be defluorinated by LAH under forced conditions.$^{54-56}$ Yet, N-(2-hydroxyethyl)fluoroacetamide and fluoroacetamide are converted to the corresponding dehalogenated amines rather readily;^{141} 4-fluoro-1-nitrobutane and 5-fluoro-1-nitropentane are prone to dehydrofluorination giving piperidine and pyrrolidine respectively.^{142} It appears that these findings are consistent with the expulsion of fluorine being assisted by the other functional group(s) of the substrate, possibly due to the formation of a new bond between fluorine and another atom.

Two other possible mechanisms involving hydride transfer have also been considered for the production of 1-cyclohexylethanol (VIII) - one is intermolecular and the other is intramolecular (see Scheme XIII). The



(23)

(24)

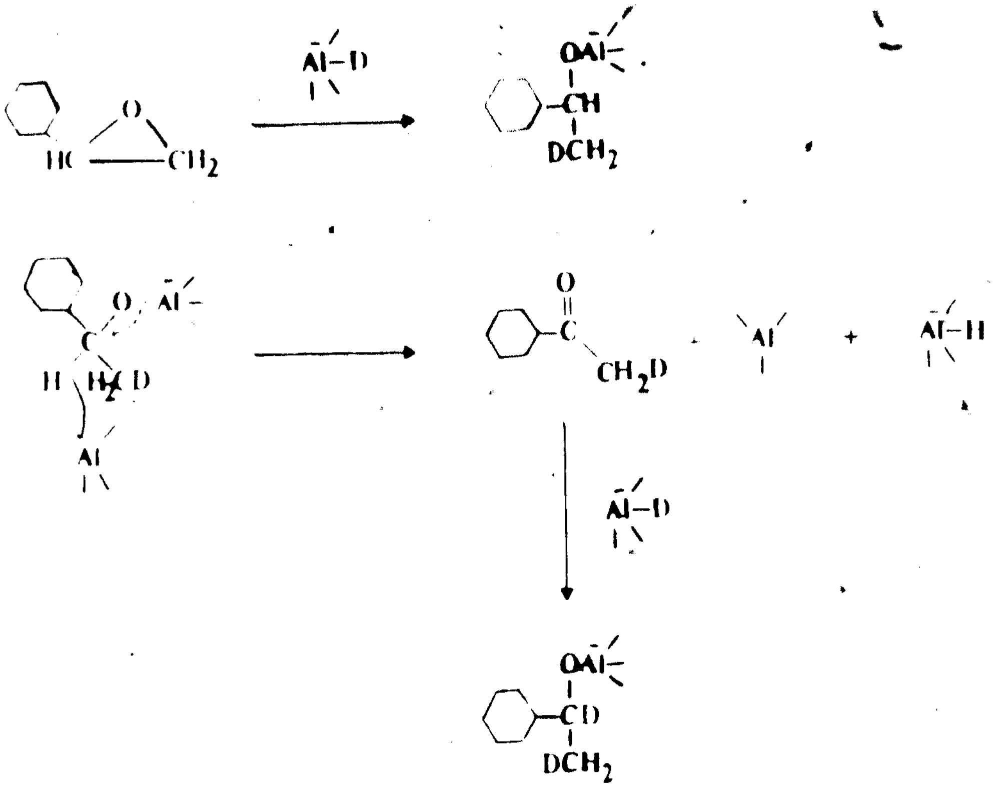
Scheme XIII

intramolecular hydride transfer cannot explain the hydride dependence of the yield of VIII while the bimolecular process shown in Equation (23) can. As a consequence, the unimolecular process can be dismissed, Intermolecular hydride transfer cannot be differentiated from the epoxide pathway as a possible route by which defluorination of VII occurs.

The detection of dideuterated secondary alcohol when VII was treated with LAD in benzene reveals yet another process contributing to the production of defluorinated alcohol. The anomalous product is formed via an epoxide intermediate which undergoes a deuteride opening followed by an oxidation-reduction sequence to introduce a second deuterium. This proposal lends some support from the observation that the same dideuterated species was formed upon the reduction of the epoxide itself (see Scheme XIV, p. 96).

III.2 The Reaction of α-Fluoroketones with Aluminum Hydride

Contrary to the previous report for the reductive dehalogenation of alkyl chlorides and bromides,[13] the defluorination of compounds I, II, VI and VII by aluminum hydride is not noticeably slow compared to the corresponding LAH reaction. This is likely attributed to the formation of an aluminum-fluorine bond.



Scheme XIV

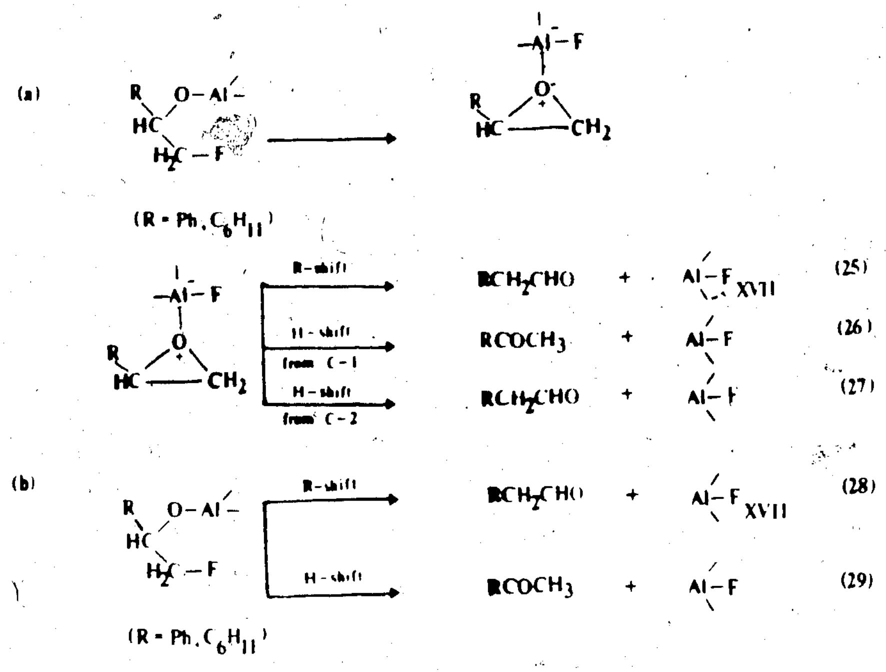
The possiblity of a radical pathway was considered for the dehalogenation of I and II since aluminum hydride had been suggested[60] as a good electron donor. The hydride dependence of the product ratio III/IV is reminiscent of the LAH reaction. Furthermore, the positions of deuteration at the major defluorinated products from the reduction with aluminum deuteride agree with those predicted by the propagation chain sequence in Scheme IX. Since it has been shown[3] that nitro compounds react only slowly with aluminum hydride, the effect of the radical inhibitor, p-dinitrobenzene, on the reaction was examined. It was found that there was little difference in the product composition whether *p*-DNB was present or not. Since inhibition was not observed, this method was unable to differentiate between homolytic and heterolytic pathways.

The formation of 1-phenylethanol (III) from the reaction of I and II was found to be faster than that of 2-phenylethanol (IV) with increasing hydride-to-substrate ratio. This resembles the reduction of styrene oxide by the hydride reagent (Table VIII). The result of a control experiment with a synthetic mixture of III and IV suggested that interconversion between the two compounds did not occur in the presence of aluminum hydride. The reduction of styrene oxide by aluminum deuteride afforded 2-phenylethanol-2-d. This observation contrasts the corresponding reaction of the fluoroalcohol II which yielded 2-phenylethanol-1-d as the major primary alcohol. The latter reaction most likely involves the intermediacy of phenylacetaldehyde. In fact, this aldehyde was detected in traces when I or II was allowed to react with a limited quantity of aluminum hydride. For the aliphatic reactants VI and VII, 2-cyclohexylethanol (IX) was obtained in low yield ($<10\%$), but the epoxide X was produced in significant quantity. When these substrates were allowed to react with aluminum deuteride, the rearranged alcohol product was deuterated chiefly at C-1, whereas the corresponding reaction of X yielded only

3% of primary alcohol which was deuterated at C-2. Again, these fluoro substrates give defluorinated rearranged alcohol which arises principally from an aldehyde intermediate.

Deuteration at C-1 of the 1-substituted-ethanol products from the reaction with aluminum deuteride signifies the existence of ketone intermediates. This is supported by the detection of acetophenone and cyclohexyl methyl ketone (XI) from the reduction of I/II and VI/VIII respectively. Two possible pathways could be proposed for the formation of the dehalogenated carbonyl compounds from the fluorohydrins: (a) via the rearrangement of an epoxide intermediate and (b) hydride and/or alkyl shift(s) of the fluoroalkoxides. These are presented in Scheme XV (p. 99).

The species XVII in Scheme XV is a derivative of aluminum fluoride and is probably a stronger Lewis acid than aluminum hydride and its alkoxy derivatives. It is well known that an epoxide rearranges, in the presence of a Lewis acid, to a carbonyl compound.[33,36,39,144] Mosher and coworkers[36] observed that the reaction of (R)-(+)-styrene oxide-2,2-d_2 by $AlCl_2H$ in the presence of aluminum chloride (i.e., LAH with 4 molar equivs of $AlCl_3$) yielded 2-phenylethanol-1,2-d_2 with low stereospecifity, which indicates ring rupture to generate a more stable carbocation. In accord with this finding, Equations (25)



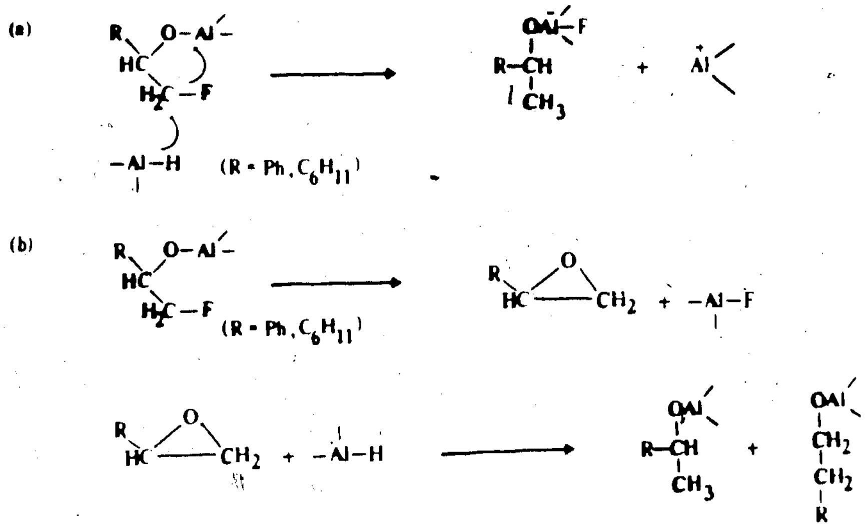
Scheme XV

and (26) in the Scheme are ruled out for R = Ph and likewise, for R = C_6H_{11} as well.

Equations (27)-(29) should be examined with the present experimental results. Regarding migratory aptitudes, there is no clearly defined relative tendencies, especially that between hydrogen and alkyl or aryl.[145] According to (28), an α-fluoroketone reacts with AlD_3 to give $D_2C(OH)CH_2R$ while the same reaction *via* (27) necessitates the formation of DHC(OH)CHDR. Only alcohols of the type $D_2C(OH)CH_2R$ were detected from the reaction of both fluoroketones I and VI. Therefore, direct phenyl rearrangement of the fluoroalkoxide during the reaction of compounds I and II provides the bulk of product IV which prevails at low hydride concentration. The yield of the rearranged alcohol IX is insignificant from the reaction of the cyclohexyl-substituted substrates, and is largely derived from cyclohexylacetaldehyde which is formed likewise from alkyl migration of the fluoroalkoxide.

If the mechanism in Scheme XV is followed, the products CH_3COR and $CH_3CD(OH)R$ can be derived from a hydride shift during the course of the reaction of fluoroalcohols II and VII with aluminum deuteride. Hydride shift is considerably less important than phenyl shift since the yield of 2-phenylethanol-1-d is much higher than the combined yield of acetophenone and 1-phenylethanol-1-d from the reduction of II with AlD_3 (Reaction (4), Table IX). On the other hand, the migration of hydrogen is preferred to the migration of cyclohexyl group as predicted from the results of the reaction of VI and VII with the deuteride reagent (Reactions (1) and (2), Table XIV).

The major source of the products 1-phenyl- and 1-cyclohexylethanols cannot be <u>via</u> (29) since $RCH(OH)CH_2D$ is the major secondary alcohol product of aluminum deuteride reduction of either fluorohydrin. At high deuteride concentration ([hydride]/[substrate] $\gtrsim 1$), 1-phenylethanol-2-d is almost the exclusive product. Two possible major paths for the formation of alcohols III and VIII can be proposed, viz, (a) from direct nucleophilic displacement and (b) from the direct opening of an epoxide intermediate. These two paths are depicted in Scheme XVI.



(30)

Scheme XVI

As with LAH, the intramolecular hydride transfer can be ruled out as the formation of III and VIII is hydride dependent. Equation (30) (path (b)) represents the reaction of an epoxide with a weak Lewis acid like AlH_3, i.e. direct ring opening by hydride transfer. This process could be intramolecular or intermolecular. The former mode of transfer, which necessarily involves a 4-centered transition state, was suggested by Ashby and Cooke[41] for the reduction of epoxide. However, intramolecular hydride transfer was disfavored by subsequent investigators.[36,43] Using excess AlD_3 (2:1), Mosher and coworkers demonstrated that (R)-(+)-styrene oxide-2,2-d_2 undergoes the reduction with high stereospecificity (Equation (9)). The result of the control experiment in the present work with styrene oxide (Table VIII) revealed that using a 3:1 molar ratio of styrene oxide to aluminum hydride, only 2% of the starting material remained after 16 h. Moreover, the product ratio of the secondary to the primary alcohols increased with the amount of hydride. As a consequence, intramolecular transfer cannot be excluded at low level of hydride. The minor quantity of the rearranged products, $HOCH_2CHDR$ or $HOCH_2CD_2R$, from the reaction of a fluoro substrate with aluminum deuteride could possibly arise from direct hydride transfer to an epoxide intermediate. However, it is dubious that 1-phenylethanol was generated from the styrene oxide intermediate (Equation (30)). The product ratio of III to IV for the reaction with excess hydride reagent was found to be much too high when compared with the ratio of the secondary to the primary alcohol products from the opening of styrene oxide with aluminum hydride. The results of the works of several investigators on the latter reaction are compiled in Table XV. In the presence of excess aluminum deuteride, 1-phenylethanol-2-d was produced almost exclusively from the reaction of II while 2-phenylethanol-2-d, which arises from an epoxide intermediate, was not detected (Reaction (3), Table IX). This observation is inconsistent with the product ratios of secondary to primary alcohols shown in Table XV. At a deuteride - to-substrate ratio of about 0.65, the AlD_3 reduction of fluoroalcohol II furnished both 1-phenylethanol-2-d and 2-phenylethanol-2-d in the ratio of about 17 to 1 (Reaction (3), Table IX). The corresponding reaction of styrene oxide produced these alcohols in the ratio of about 1.3 to 1 (Reaction (2), Table VIII). On the basis of the product yields, Equation (30) likely represents, at most, only a minor route for the generation of 1-phenylethanol (III). Consequently, direct nucleophilic displacement ((a), Scheme XV) is favored as the major pathway.

Of course, the same conclusion can hardly be extended to the cyclohexyl substrates VI and VII since epoxide X is a product. Furthermore, the primary alcohol produced from the reduction of epoxide X was in much lower yield

Table XV

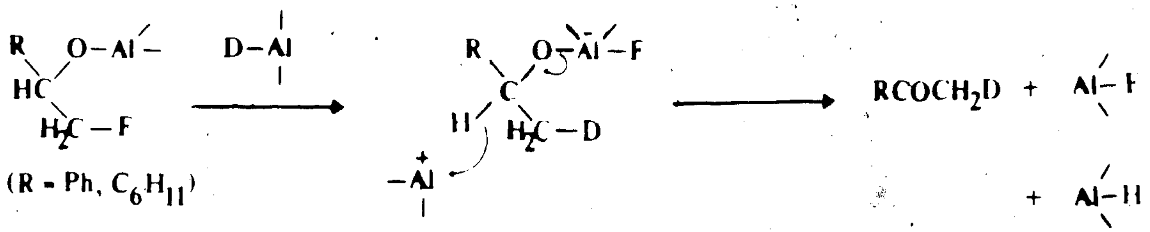
Reaction of styrene oxide (V) with excess aluminum hydride

Entry	Mole AlH_3/V	Reaction Conditions	Product Composition, %		Yield ratio III/IV	Ref.
			$PhCH(OH)CH_3$(III)	$PhCH_2CH_2OH$(IV)		
1	1	THF/25°/1 h	73(76)[a]	27(24)[a]	2.7(3.2)[a]	2
2	3	THF/rt/2 h	74	26	2.8	45
3[b]	2	Et_2O/0°/0.5 h	49.9[c]	50.1[d]	1.0	36

[a] The value in parenthesis refers to one under reaction condition of THF/0°/1 h.
[b] Aluminum deuteride and styrene oxide-2,2-d_2 were used.
[c] The product was 1-phenylethanol-2-d.
[d] The product was 2-phenylethanol-2-d.

compared to that of the isomeric secondary alcohol - a trend which is consistent with the product composition from the reaction of VI and VII. The alternate path, i.e. direct nucleophilic displacement, cannot be dismissed for the generation of alcohol VIII.

The unexpected deuterated products, DCH_2COR and the related $DCH_2CD(OH)R$, were detected in the reaction of fluoroalcohols II and VII with aluminum deuteride, but not in the corresponding reaction of epoxide X. One possible explanation, which is related to path (a), Scheme XVI, is offered below:



(31)

(31) could be a concerted process, instead of a stepwise one as shown.

III.3 Conclusions

Both LAH and aluminum hydride reductions of α-fluoroketones proceed by a heterolytic hydride transfer process to the corresponding fluoroalkoxides. Subsequent reaction of the latter yields dehalogenated products. The defluorination of the alkoxide derivative of 2-fluoro-1-phenylethanol by LAH proceeds via an electron transfer process as one of the steps in the radical chain propagation sequence. Depending on the amount of the hydride reagent relative to the reactant, the radical species (XIV, Scheme IX) resulted from this process may either abstract a hydrogen atom from an aluminohydride species or rearrange to a more stable radical species (XV). Since the alkoxide derived from 1-cyclohexyl-2-fluoroethanol cannot follow this pathway, its dehalogenation was proposed to proceed via an intramolecular process giving rise to an epoxide, which could be reduced by the hydride reagent. Intermolecular hydride transfer to the fluoroalkoxide cannot be precluded as an alternate route from which 1-cyclohexylethanol is produced. Similar mechanistic conclusion can be extended to the reduction of the aliphatic substrate by aluminum hydride. It appears that the defluorinated products from the reduction of the aromatic fluoroalkoxide with aluminum hydride do not arise from an epoxide intermediate. 1-Phenylethanol probably comes from an intermolecular hydride transfer to the fluoroalkoxide. 2-Phenylethanol is originated primarily from the phenyl migration of the alkoxide. Not only does phenyl group migrates at the fluoroalkoxide stage, hydride and cyclohexyl shifts are also detectable. Yet the latter migrations represent only minor pathways leading to defluorinated products.

EXPERIMENTAL

IV.1 Materials

Benzene (J.T. Baker Chemical Co. or Aldrich Chemical) was purified[158] by stirring with aluminum chloride, then dried over calcium hydride and distilled. The process was repeated once, the final distillation being carried out over lithium aluminum hydride. Fractional recrystallization of the distillate afforded a fraction of 99.99% purity (Glpc analysis).

Tetrahydrofuran (Terochem) was predried over KOH or NaOH pellets and distilled over LAH. The distillate was stored at refluxing temperature with sodium benzophenone ketyl and freshly redistilled prior to use.

Lithium aluminum hydride (Alfa Products, 95%) was used as obtained when the reactions were carried out in benzene, since the results of using purified and nonpurified reagent were shown to be comparable (see Reactions 10 and 11, Table I). In THF, a filtered solution of the reagent was used. Similarly, lithium aluminum deuteride (Aldrich Chemical, 98 atom % D) was used as obtained when the reactions were carried out in benzene and allowed to dissolve when employed in THF.

1,4-Di-*tert*-butylbenzene (Aldrich Chemical) was recrystallized from a mixture of Skelly B and ethanol (1:1 v/v) and dried in vacuo: mp 79-80° (lit[146] 80-81°).

1-Phenylethanol, 2-phenylethanol and styrene oxide (Aldrich Chemical) were distilled before use. Glpc analysis showed them to be >99% pure.

Acetophenone (Koch-Light Laboratories) was also distilled before use. Glpc analysis showed it to be >99.5% pure.

Phenylacetaldehyde (J.T. Baker Chemical Co., 50% ethanolic solution) was distilled before use.

Tetradecane (Eastman Organic Chemicals) was distilled before use. Glpc analysis showed it to be >99.98% pure.

Bibenzyl (Eastman Organic Chemicals) was recrystallized from methanol and dried in vacuo: mp 48-49.5° (lit[146] 52.3°).

1,3-Dinitrobenzene (Aldrich Chemical) was purified by recrystallizing from methanol and dried in vacuo: mp 89.5-90° (lit[146] 90°). 1,4-Dinitrobenzene (Aldrich Chemical) was used directly without further purification.

1,4-Dicyanobenzene (Aldrich Chemical) was purified by sublimation: mp 218-220° (lit[146] 222°).

Dicyclohexylphosphine (Aldrich Chemical) was used directly without further purification.

α,α'-Azobisisobutyronitrile (Aldrich Chemical) was recrystallized from a mixture of ethanol and water (1:1 v/v) and dried in vacuo: mp 101-102° (lit[147] 103°).

Fluoroacetic acid was prepared from fluoroacetamide (50.0 g, 0.65 mole). The procedure was modelled on that reported by Buckle and coworkers.[148] Instead of using arsenous oxide and nitric acid, a mixture of nitric oxide and nitrogen dioxide was bubbled onto fluoroacetamide crystals. After the excess nitrous fumes were expelled, distillation afforded a colorless liquid (32.1 g, 64%): bp 164-165°/700 mm; mp 26-27°; 80 MHz ^1H nmr ($CDCl_3$) δ 5.18 (d, J = 46.7 Hz, 2H), 9.37 (s, 1H); ir (neat) 1850 (CO stretching), 3240 cm^{-1}.

Fluoroacetyl chloride was produced from the reaction of fluoroacetic acid (34.1 g, 0.44 mole) and α,α,α-trichlorotoluene (94.5 g, 0.48 mole) in the presence of zinc chloride (catalytic amount).[149] Distillation from the reaction mixture gave an oily liquid (36.2 g, 86%):

bp 71-73.5°; 80 MHz ^{1}H nmr (CDCl$_3$) δ 5.34 (d, *J* = 46.7 Hz); ir (neat) 1750 (CO stretching), 3100 cm^{-1}.

α-Fluoroacetophenone (I) was obtained from the reaction of benzene (10 mL, 0.11 mole) with a mixture of fluoroacetyl chloride (10.8 g, 1.11 mole) and aluminum chloride (31 g) in dichloromethane using the method of Bergmann and Kalmus.[129] Upon treatment with hydrochloric acid, the solvent was removed (in vacuo) to yield a dark reddish-brown liquid. Fractional distillation afforded a colorless liquid (10.5 g, 68%) which solidified at room temperature: bp 72-75°/2 mm (lit[129] 65-70°/1 mm); 200 MHz ^{1}H nmr (CDCl$_3$) δ 5.36 (d, *J* = 46.0 Hz, 2H), 7.26 (t, *J* = 1.6 Hz, 2H), 7.32-7.50 (m, 1H), 7.66 (d, *J* = 1.6 Hz, 2H); ir (neat) 1710 cm^{-1}; mass spectrum *m/e* (relative intensity) 138 ($M^{+\cdot}$, 15.2), 105 (100.0), 77 (64.5).

Anal. Calcd for C_8H_7OF: C, 69.56; H, 5.11. Found: C, 69.88; H, 5.19.

2,4-Dinitrophenylhydrazone: orange needle (recrystallized from *p*-xylene), mp 213-214° (lit[129] 213-214°). *Anal.* Calcd for $C_{14}H_{11}N_4O_4F$: C, 52.84; H, 3.48; N, 17.61. Found: C, 52.83; H, 3.54; N, 17.26.

2-Fluoro-1-phenylethanol (II) was prepared from the reduction of ketone I with sodium borohydride. A solution of I (5.0 g, 0.036 mole) in diethyl ether (30 mL) was added slowly to a stirring mixture of sodium borohydride (2.0 g, 0.053 mole), diethyl ether (100 mL) and water (5 mL). Stirring continued at room temperature for 5 h and the starting material was all consumed (checked by glpc). The reaction mixture was poured into cold dilute hydrochloric acid. The organic layer was separated while the aqueous layer was extracted with diethyl ether (2 x 50 mL). Combined organic layer was washed with water, sodium bicarbonate solution (5%) and finally, with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo. Fractional distillation using a Vigreux column afforded a colorless liquid in the largest fraction (bp 110-111°/15 mm) which contained 10-15% minor components (glpc). The major product was separated by liquid chromatography with an alumina-packed column, the eluting solvent system being a mixture of Skelly B and ethyl acetate (80:20 v/v). The purity was over 99.5% (glpc): 80 MHz ^{1}H nmr ($CDCl_3$) δ 3.38 (s, 1H), 4.43 (d of m, $\underline{J_d}$ = 48 Hz, 2H), 4.75-5.13 (m, 1H), 7.34 (s, 5H); ir (neat) 3370 cm^{-1}; mass spectrum m/e (relative intensity) 140 ($M^{+\cdot}$, 29.2), 107 (100.0), 79 (55.7).

Anal. Calcd for C_8H_9OF: C, 68.56; H, 6.47. Found: C, 68.34; H, 6.54.

Fluoroacetonitrile was prepared using the procedure of Buckle and coworkers.[148] Fluoroacetamide (33.0 g, 0.43 mole) was pre-dried in vacuo over concentrated sulfuric acid. It was allowed to mix with phosphorous pentoxide (60.0 g, 0.42 mole) in a three-neck round bottom flask fitted with mechanical stirring device. The stirring mixture was heated to 110-120° and a colorless liquid (13.1 g, 52%) was obtained by distillation: bp 78-80° (lit[149] 80°/760 mm); 80 MHz ^1H nmr ($CDCl_3$) δ 5.00 (d, J = 46.0 Hz); ir (CCl_4) 910, 1050 cm^{-1}.

The conversion of fluoroacetonitrile (8.0 g, 0.13 mole) to *cyclohexyl fluoromethyl ketone (VI)* was effected by the addition reaction with cyclohexylmagnesium bromide according to the method of Bergmann *et al.*[150] The Grignard reagent was prepared in situ from magnesium turnings (3.3 g, 0.14 mole) and cyclohexyl bromide (22.1 g, 0.13 mole) in diethyl ether. Fractional distillation of the crude product (reddish brown liquid) furnished a colorless liquid (77-79°/15 mm, lit[151] 82-83°/20 mm). About 10% (glpc, by area) of a minor component, identified to be dicyclohexyl, was detected and removed by liquid chromatography using an alumina-packed column. The eluting solvent was Skelly B followed by an increasing fraction of ethyl acetate to about 20%. 200 MHz ^1H nmr

($CDCl_3$) δ 0.93-1.33 (m, 5H), 1.43-1.79 (m, 5H), 2.32-2.54 (m, 1H), 4.72 (d, J = 47.0 Hz, 2H); ir (neat) 1740, 2940 cm^{-1}; mass spectrum m/e (relative intensity) 166 (2.3), 144 ($M^{+\cdot}$, 8.1) 83 (100.0) 55 (73.0).

Anal. Calcd for $C_8H_{13}OF$: C. 66.64; H, 9.09. Found: C, 66.17; H, 9.13 (The compound may still contain a small amount of impurity. The 2,4-DNP derivative was prepared).

2,4-dinitrophenylhydrazone: yellow needle (recrystallized from methanol), mp 129.5-130.5° (lit[150] 125-127° prism). *Anal.* Calcd for $C_{14}H_{17}N_4O_4F$: C, 51.85; H, 5.28; N, 17.[illegible]8. Found: C, 51.54; H, 5.32; N, 16.97.

1-Cyclohexyl-2-fluoroethanol (VII) was prepared from the reduction of ketone VI (5.0 g, 0.035 mole) with sodium borohydride (2.0 g, 0.053 mole) following the same procedure as for the conversion of ketone I to alcohol II. Fractional distillation using a Vigreux column afforded a colorless liquid (97-98°/17 mm). The purity was >99% (glpc): 200 MHz ^1H nmr ($CDCl_3$) δ 0.61-2.03 (m, 11H), 2.91 (s, 1H), 3.35-3.60 (m 1H), 4.33 (d of m, J_d = 48.0 Hz, 2H); ir (vapor) 2875, 2930, 3680 cm^{-1}; mass spectrum m/e (relative intensity) 113 (41.0), 95 (74.1), 55 (100.0).

1-Cyclohexylethanol (VIII) was produced from the reaction of cyclohexylmagnesium chloride and acetaldehyde in diethyl ether.[152] Fractional distillation furnished a colorless liquid (72-74°/15 mm). About 10% (glpc) of two minor components, identified to be dicyclohexyl and cyclohexanol, were detected and removed by liquid chromatography using an alumina-packed column. The eluting solvent was a mixture of Skelly B and ethyl acetate. 200 MHz ^1H nmr ($CDCl_3$) δ 0.67-1.29 (m, 9H; contains 3H, d, 1.09 ppm, J_d = 6.0 Hz), 1.47-1.85 (m, 5H), 2.63 (s, 1H) 3.34-3.52 (m, 1H); ir (neat) 2920, 3375 cm^{-1}; mass spectrum m/e (relative intensity) 110 (40.5), 95 (21.2), 45 (100.0).

2-Cyclohexylethanol (IX) was prepared from the reaction of cyclohexylmagnesium bromide and ethylene oxide in diethyl ether.[153] Fractional distillation afforded a colorless liquid (bp 85.5-87°/15 mm; lit[146] 87°/15 mm). The minor components, identified to be dicyclohexyl and cyclohexanol, were removed in the same way as described for the purification of 1-cyclohexylethanol. 400 MHz ^1H nmr (C_6H_6) δ 0.80-1.03 (m, 2H), 1.04-1.35 (m, 3H), 1.35-1.54 (m, 3H), 1.55-1.83 (m, 5H), 3.61 (t, J = 6.5 Hz, 2H), 4.10 (s, 1H); ir (vapor) 2930, 3660 cm^{-1}; mass spectrum m/e (relative intensity) 110 (49.9), 95 (16.9), 82 (100.0), 81 (96.5).

Cyclohexyl methyl ketone (X) was prepared from the oxidation of a benzene solution of alcohol VIII with an aqueous solution of sodium dichromate dihydrate and sulfuric acid.[154] Fractional distillation furnished a colorless liquid: bp 68-69°/18 mm (lit[155] 57-60°/8 mm); 80 MHz ^1H nmr ($CDCl_3$) δ 1.00-2.13 (m, 10H), 2.13 (s, 3H), 2.13-2.60 (m, 1H); mass spectrum m/e (relative intensity) 126 ($M^{+\cdot}$, 52.9), 111 (19.5), 55 (100.0).

1-Cyclohexyl-1,2-epoxyethane (XI) was obtained from the reaction of vinylcyclohexane with m-chloroperbenzoic acid.[156] Fractional distillation afforded a colorless liquid: bp 62-64°/15 mm (lit[157] 40-41°/6 mm); 80 MHz ^1H nmr ($CDCl_3$) δ 0.60-2.25 (m, 11H), 2.38-2.83 (m, 3H); ir (neat) 859, 1459, 2863 cm^{-1}; mass spectrum m/e (relative intensity) 126 ($M^{+\cdot}$, 3.7), 96 (76.3), 81 (100.0).

IV.2 Instrumentation

All melting point values were measured with a Mel-Temp melting point apparatus and were uncorrected. All boiling point values were also uncorrected.

400 MHz ^{1}H nmr spectra were recorded using a Bruker WH-400 NMR spectrometer. 200 MHz ^{1}H and ^{2}H nmr spectra were obtained on a Bruker WH-200 NMR spectrometer. 80 MHz ^{1}H nmr spectra were obtained on Bruker WP-80 NMR spectrometer. Infrared spectra were recorded on a Nicolet 7199 FT-IR spectrophotometer. Mass spectra were obtained using an AEI MS-12 medium resolution mass spectrometer coupled to a Data General Nova 3 DS-55. Gas chromatography - mass spectra (glpc-ms) data were obtained using a Varian Aerograph 1400 gas chromatograph coupled to an AEI MS-12 mass spectrometer with a Data General Nova 3 DS-55. Gas chromatography - infrared spectra (glpc-ir) data were obtained using a Nicolet 7199 FT-IR spectrometer interfaced to a Varian 3700 gas chromatograph. The column for glpc-ms and glpc-ir analyses was the same as for glpc analysis (see Section IV.3).

Glpc analyses with packed columns were carried out using a Carlo Erba gas chromatograph equipped with a flame ionization detector and coupled to a vista CDS 401 chromatography Data System. The detector was calibrated using a mixture of synthetic materials and an internal standard.

IV.3 Procedures for Reactions

H-shaped Pyrex reaction ampoule for degassed reactions were joined to 10/30 joints. The ampoules had been cleaned with chromic acid solution, water, ammonia water, distilled water and just prior to use, oven-dried at about 120° for at least eight hours.

Preparation of a solution (A) of lithium aluminum hydride (LAH) in tetrahydrofuran (THF) and the assay of its hydride equivalence[2] Commercial LAH was added to a three-neck round-bottom flask (250 mL) containing purified THF (200 mL). The mixture was stirred under a nitrogen atmosphere for over 2 h at room temperature. It was filtered through a sintered glass funnel under nitrogen atmosphere inside a glove box. The filtered solution was clear. It was capped with a silicone syringe septum and stored in the glove box.

A quantity (1 mL) of Solution A was injected into a three-neck round-bottom flask fitted with a syringe septum and containing a stirring mixture of 1:1:1 (by volumes) of water, THF and glycerine. The gas (hydrogen) liberated was collected over mercury inside a graduated buret connected to a reservoir which was open to the atmosphere. The volume of gas was determined from the displacement of mercury at atmospheric pressure. The hydride equivalence of the solution was thus calculated using the ideal gas equation. Over various batches of similar proportions of LAH to THF, this value was in the range of 1.15-1.50 M and did not change by more than 5% within a period of two weeks.

Preparation of a solution of aluminum hydride in THF (Solution B) and the assay of its hydride equivalence.[13]

A clear solution of LAH in THF (Solution A, 140 mL, hydride equivalence = 1.47 M) was stirred under a nitrogen atmosphere in a three-neck round bottom flask (250 mL) fitted with a condensor containing crushed dry ice and capped with a syringe septum. This was cooled in an ice-water bath. Sulfuric acid (1.43 mL, ca. 25.8 mmole) was injected slowly into the mixture. Gas flow increased, accompanied by the precipitation of a white solid. When the gas flow resumed to the original rate, stirring of the mixture was allowed to continue at ambient temperature for at least another 2 h. The mixture was allowed to stand under a dry nitrogen atmosphere for eight additional hours. The solution was filtered through a sintered glass funnel inside a glove box. The slightly turbid solution was capped with a silicone syringe septum and kept in the dry box until use.

The hydride strength of the solution (B) was determined in the same manner as the assay of LAH in THF.[2] For a number of preparations of Solution B from solutions of LAH/THF of comparable concentrations, the hydride equivalence was in the range of 0.80-1.25 M and did not change by more than 5% within a period of two weeks.

General procedure for the reaction with LAH in benzene. Lithium aluminum hydride was transferred to one arm of an H-shaped reaction vessel together with an aliquot of benzene. An aliquot of a stock solution of a substrate and an internal glpc standard (*p*-di-*tert*-butylbenzene for the aromatic substrates I, II and V; and tetradecane or bibenzyl for the cyclohexyl-substituted substrates VI, VII and X) was pipeted into the other arm of the ampoule. The reaction vessel was degassed three times by the freeze-thaw technique, sealed and thermostated at 61° before the materials in both arms were mixed. The freeze-thaw step was bypassed if the reaction was carried out in the presence of air. The reaction ampoule was kept at 61° for the desired period of time. It was then frozen, opened and the mixture was treated with an aliquot of dilute sulfuric acid (<0.5 M) saturated with sodium chloride. The aqueous layer was separated and extracted with benzene. The combined organic layer was dried over anhydrous potassium carbonate. The product mixture was analyzed by glpc (70-180°) using a 1/4" x 10' stainless steel column containing 10% FFAP on Chromosorb W, AW DMCS. The products were identified by comparing their retention times with those of the authentic materials and by a comparison of their ir (glpc-ir) and mass spectra (glpc-ms) with those of the authentic materials. The yields were determined against the internal standard utilizing the following expression:

$$\text{moles component } i = \frac{\text{Area integration corresponding to } i}{\text{Area integration corresponding to std}} \times CF_i \times \text{mole std}$$

where CF_i is the calibration factor of component i obtained from the analysis of a standard calibration mixture composed of known quantities of authentic samples and the standard.

$$CF_i = \frac{(\text{moles component } i/\text{moles std}) \text{ in the calibration mixture}}{(\text{area integration due to } i/\text{area integration due to std})}$$

When the reaction was carried out in the presence of α',α'-azobisisobutyronitrile (4-7 mole % of substrate), the additive was weighed and added to the compartment of the reaction ampoule containing the substrate. When the reaction was carried out in the presence of m-DNB, p-DNB, DCB or DCPH (3-6 mole % of substrate), an aliquot of benzene solution of the additive was pipeted into the compartment of the reaction ampoule containing the substrate. In either case, subsequent steps were identical to those described in the preceding paragraph.

General procedure for the reaction with LAH in THF. The procedure followed closely that for the reaction with LAH in benzene, except that an aliquot of Solution A of known concentration was syringed into one arm of the H-shaped ampoule together with an aliquot of THF.

The procedure for the analysis of the reaction mixture from the reaction of a cyclohexyl-substitued substrate (VI, VII or X) was slightly modified since X in THF had been shown to be sensitive to dilute mineral acid at room temperature. The reaction mixture was treated with an aliquot of benzene before the addition of dilute sulfuric acid. Subsequent steps were not modified.

General procedure for the reaction with aluminum hydride in THF. The procedure followed that for the reaction with LAH in THF. An aliquot of Solution B of known concentration was syringed into one arm of the H-shaped reaction ampoule together with an aliquot of THF, and this mixture was allowed to react with the substrate.

The reaction with lithium aluminum deuteride (LAD) in benzene. The procedure resembled to the general procedure for the LAH reaction in benzene. The reaction mixture was allowed to stand at 61° for 16 h. It was analyzed by its ^1H and ^2H nmr spectra - the products were identified with the aid of the ^1H nmr spectra of synthetic samples and their relative composition was determined from the integrations of the spectra and glpc molar ratios. The analyzed results for the reaction of substrates I, II and V ~~are pr~~esented in Table IV, and for the reaction of substrates VI, VII and X, in Table XI.

(a) Ketone I. See Figure 1. 200 MHz ^1H nmr (C_6H_6) δ 1.24 (broad s), 2.51 (s), 4.08 (d, J = 47.0 Hz); 200 MHz ^2H nmr (C_6H_6) δ 1.24, 3.42, 4.49.

(b) Alcohol II. See Figure 2. 200 MHz ^1H nmr (C_6H_6) δ 1.24-1.37 (m), 2.59 (d, J = 7.0 Hz), 2.78 (hydroxylic proton), 3.20 (hydroxylic proton), 3.44-3.60 (m,), 3.94 (hydroxylic proton), 4.00-4.36 (d of m, J_d = 47.0 Hz), 4.55-4.80 (m); 200 MHz ^2H nmr (C_6H_6) δ 1.25, 3.47, 4.55. Glpc-ms analysis of the reaction sample revealed the presence of traces of phenylacetaldehyde.

(c) Epoxide V. 200 MHz ^1H nmr (C_6H_6) δ 1.30 (d of m, J_d = 6.0 Hz), 2.28-2.35 (m), 2.54-2.65 (m), 3.40-3.47 (m), 3.52 (d, J = 6.0 Hz), 4.59 (t, J = 6.7 Hz); 200 MHz ^2H nmr (C_6H_6) δ 1.29, 2.55.

(d) Ketone VI. 200 MHz ^1H nmr (C_6H_6) δ 0.71-1.32 (m; contains a broad s at 0.97 ppm) 1.46-1.87 (m), 4.09 (d, *J* = 47.3 Hz); 200 MHz ^2H nmr (C_6H_6) δ 0.97, 3.27, 7.15 (C_6H_5D).

(e) Alcohol VII. 200 MHz ^1H nmr (C_6H_6) δ 0.96-1.28 (m), 1.34-1.45 (m), 1.45-1.84 (m), 3.22-3.37 (m), 4.12 (d of m, *J* = 48.0 Hz); 200 MHz ^2H nmr (C_6H_6) δ 0.97, 3.24, 7.15 (C_6H_5D).

(f) Epoxide X. 200 MHz ^1H nmr (C_6H_6) δ 0.74-1.29 (m), 1.46-1.91 (m), 3.29-3.45 (m); 200 MHz ^2H nmr (C_6H_6) δ 0.89, 3.23.

The reaction with LAD in THF. A solution of LAD (0.58 g, 13.8 mmole) in tetrahydrofuran was prepared in the same way as that of Solution A. The deuteride equivalence was found to be 0.95-1.15 M for several individual preparations.

The procedure followed that for the hydride reaction in THF. The reaction mixture was allowed to stand at 61° for 16 h. It was analyzed by its ^1H and ^2H nmr spectra by comparing with the ^1H nmr spectra of synthetic samples. The relative product composition was determined from the nmr integrations and glpc molar ratios. The analyzed results for the reaction of substrates I, II and V are shown in Table IV, and for the reaction of substrates VI, VII and X, in Table XI.

(a) Ketone I. 200 MHz ^1H nmr (C_6H_6) δ 1.26 (broad), 3.98 (m), 4.22 (d, J = 47.3 Hz); 200 MHz ^2H nmr (C_6H_6) δ 1.21, 4.45, 7.15 (C_6H_5D).

(b) Alcohol II. 200 MHz ^1H nmr (C_6H_6) δ 1.26 (broad), 4.20 (d of d, J = 48.0, 5.3 Hz), 4.53 (t, J = 5.3 Hz); 200 MHz ^2H nmr (C_6H_6) δ 1.24, 7.16 (C_6H_5D). Glpc analysis of the product mixture revealed a trace quantity of the product whose retention time corresponded to that of 2-phenylethanol.

(c) Epoxide V. 200 MHz ^1H nmr (C_6H_6) δ 1.29 (d of t, J_d = 6.3 Hz, $J_t \approx$ 2 Hz), 2.49-2.65 (broad s), 2.60-3.06 (broad s), 3.36-3.61 (m, partly due to residual THF), 4.60 (t, J = 6.0 Hz); 200 MHz ^2H nmr (C_6H_6) δ 1.26, 2.50, 7.15 (C_6H_5D).

(d) Ketone VI. 200 MHz ^2H nmr (C_6H_6) δ 0.78-1.36 (m, contains a broad s at 1.00 ppm), 1.32-1.60 (m), 1.40-1.98 (m), 2.64 (broad s, hydroxylic proton), 4.22 (d of m, J_d 47.3 Hz); 200 MHz ^2H nmr (C_6H_6) δ 0.97, 3.27, 7.15 (C_6H_5D).

(e) Alcohol VII. See Figure 4. 200 MHz ^1H nmr (C_6H_6) δ 0.78-1.42 (m; contains a d of t at 1.05 ppm, J_d = 6.7 Hz, $J_t \approx$ 2 Hz), 1.30-1.60 (m), 1.34-1.98 (m), 2.23-2.25 (d, hydroxylic proton), 2.93 (d, hydroxylic proton), 3.32-3.50 (m), 4.22 (d of m, $\underline{J}_d$ = 47.3 Hz); 200 MHz ^{2}H nmr (C_6H_6) δ 1.03, 3.35, 7.15 (C_6H_5D).

(f) **Epoxide X.** 200 MHz ^{1}H nmr (C_6H_6) δ 0.85-1.38 (m; contains a d of t at 1.03 ppm, $\underline{J}_d$ = 6.7 Hz, $\underline{J}_t$ ≈ 2 Hz), 1.58-1.99 (m), 3.15-3.49 (m); 200 MHz ^{2}H nmr (C_6H_6) 0.97, 7.15 (C_6H_5D).

The reaction with aluminum deuteride in THF. A solution of aluminum deuteride in THF was prepared and assayed in the same way as that of Solution B.[13]

The procedure followed that for the hydride reaction. The reaction mixture was analyzed by ^{1}H and ^{2}H nmr spectroscopy and assisted by glpc-ms and glpc-ir. The relative product composition was determined from the nmr integrations and glpc molar ratios. The analyzed results for the reaction of substrates I, II and V are found in Table IX, and for the reaction of substrates VI, VII and X, in Table XIV.

(a) Ketone I. The ketone (0.57 mmole) in THF (2 mL) was mixed with an aliquot (2 mL) of the deuteride solution (1.10 M in deuteride equivalence) at 61° and allowed to react for 3 h. 200 MHz ^{1}H nmr (C_6H_6) δ 1.24 (broad), 2.52 (s), 3.47 (s), 4.18 (d, $\underline{J}$ = 46.0 Hz), 4.67 (d, $\underline{J}$ = 48.0 Hz); 200 MHz ^{2}H nmr (C_6H_6) δ 1.26, 2.51, 3.43, 4.50.

An identical run was carried out for a lower concentration of the substrate (0.34 mmole ketone in 2 mL THF with 2 mL of deuteride solution of 1.90 M in deuteride equivalence). 200 MHz ^{1}H nmr (C_6H_6) δ 1.25 (t, $J \approx 2$ Hz), 2.22 (broad s), 2.55 (s), 3.50 (s); 200 MHz ^{2}H nmr (C_6H_6) δ 1.24, 2.50, 3.44, 4.50.

(b) Alcohol II. The alcohol (1.3 mmole) in THF (2 mL) was mixed with a THF solution of the deuteride reagent (7.4 mL, deuteride equivalence = 0.34 M) at 61° and allowed to react for 16 h. See Figure 3B for nmr spectra of the product mixture. 200 MHz ^{1}H nmr (C_6H_6) δ 0.72-0.94, 1.24-1.37 (m), 2.02-2.13 (m), 2.64 (d, J = 6.7 Hz), 3.04 (broad s), 3.48-3.69 (m), 4.06-4.38 (d of m, J_d = 47.0 Hz), 4.66 (t, J = 6.0 Hz); 200 MHz ^{2}H nmr (C_6H_6) δ 0.77, 1.30, 2.02, 2.57, 3.53, 4.60; glpc-ms corresponding to 2-phenylethanol showed that the relative intensity of m/e 123 (26.8) was higher than that of authentic 2-phenylethanol (3.3), but m/e 124 was absent; glpc-ms corresponding to 1-phenylethanol also showed that m/e 124 was absent, glpc-ms corresponding to phenylacetaldehyde and/or acetophenone showed that both m/e 105 and 91 were present; glpc-ir ν_{max} 1670 cm^{-1} (CO stretching of acetophenone).

An identical run was conducted with a higher mole ratio of the alcohol to the deuteride reagent (0.56 mmole alcohol in 2 mL THF and 2 mL of deuteride solution of 1.57 M in deuteride equivalence). See Figure 3A for the nmr spectra of the product mixture. 200 MHz ^1H nmr (C_6H_6) δ 1.26 (d of t, J_d = 6.7 Hz, J_t ≈ 2 Hz), 1.47 (broad s), 2.56 (d, J = 6.0 Hz), 3.41-3.55 (m), 4.54 (t, J = 6.7 Hz); 200 MHz ^2H nmr (C_6H_6) δ 1.26.

(c) Epoxide V. 200 MHz ^1H nmr (C_6H_6) δ 1.26 (d of t, J_d = 6.7 Hz, J_t ≈ 2 Hz), 2.57 (d, J = 6.0 Hz), 4.58 (t, J = 6.7 Hz); 200 MHz ^2H nmr (C_6H_6) δ 1.26, 2.55.

(d) Ketone VI. See Figure 5. 200 MHz ^1H nmr (C_6H_6) δ 0.71-1.40 (m; contains a broad s at 0.97 ppm), 1.42 (s), 1.51-2.18 (m), 2.57 (broad), 2.71 (broad), 3.22-3.44 (m), 3.44-3.76 (m), 4.30 (d, J = 48.0 Hz); 200 MHz ^2H nmr (C_6H_6) δ 0.81, 0.97, 1.28, 1.68, 3.29, 3.41, 7.15 (C_6H_5D).

(e) Alcohol VII. 200 MHz ^1H nmr (C_6H_6) δ 0.70-1.30 (m), 1.46-1.90 (m), 2.04 (broad s), 3.17-3.40 (m), 3.40-3.68 (unresolvable m), 4.16 (d of m, J_d = 48.0 Hz); 200 MHz ^2H nmr (C_6H_6) δ 0.82, 0.97, 1.69, 3.28, 3.40, 7.15 (C_6H_5D).

(f) Epoxide X. 200 MHz ^1H nmr (C_6H_6) δ 0.80-1.42 (m; contains a d of t at 1.04 ppm, J_d = 6.7 Hz, J_d ≈ 2 Hz), 1.47-1.95 (m), 3.27-3.47 (m), 3.48-3.62 (m); 200 MHz ^2H nmr (C_6H_6) δ 0.97, 1.35, 7.15 (C_6H_5D).

Control experiments. The following control experiments were carried out.

Since lithium hydride is the major impurity in commercial lithium aluminum hydride, the test for reaction between lithium hydride and each of compounds I, II, VI and VII was conducted. Lithium hydride (1.7-1.8 mmole) was transferred to one limb of an H-shaped reaction ampoule together with an aliquot (2 mL) of THF. An aliquot (2 mL) of a stock solution of a substrate (I, II, VI or VII; 0.60-0.75 mmole) and an internal standard for glpc analysis was pipeted into the other limb of the ampoule. Subsequent steps were identical to the general procedure for the reaction with LAH in THF. Upon standing for 16 h, the mixture was analyzed by glpc. In each case with a different substrate, it was found, within experimental errors, the molar ratio of the starting substrate to the internal standard remained constant upon the test. No new material was developed.

To test if the lithium salt of alcohol II reacted with ketone I, lithium hydride (2.52 mmole) was added to a culture tube (13 x 100 mm) into which an aliquot (4 mL) of a THF solution of alcohol II (0.36 M) and the glpc standard, *p*-di-*tert*-butylbenzene (0.078 M), was introduced. After standing at room temperature for five minutes with constant shaking, the solid residue was removed by filtration through glass wool. An aliquot (1 mL) of the filtrant was transferred to one side of an H-shaped reaction ampoule. The other side of the vessel was added an aliquot (1 mL) of a THF solution of I (0.36 M). The reaction vessel was degassed, sealed and thermostated at 61° before the materials were mixed. After standing at this temperature for 17 h, the vessel was opened and treated with dilute acid. The dried mixture was analyzed by glpc, employing the routine conditions. Within experimental errors, the molar ratio of alcohol II to the standard was constant upon the treatment. Mmole of ketone I was calculated from the glpc area integration ratio relative to the standard, its calibration factor and mmole standard (p. 119). It was found to be 0.33 mmole or 92% of added quantity. No new material was developed.

The sensitivity of epoxides V and X toward dilute sulfuric acid was tested as V and X are possible products from the reactions studied and they could be affected during the work-up of the reactions by the dilute acid. An aliquot of a stock benzene solution of epoxide V and p-di-tert-butylbenzene (glpc standard) was added to a culture tube (13 x 100 mm) into which a quantity of dilute sulfuric acid (<0.5 M) was introduced. The mixture was shaken continually for about five minutes. The organic layer was separated and dried over anhydrous potassium carbonate. The same steps were repeated for a THF solution of V and p-di-tert-butylbenzene. In either case, it was found by glpc analysis, that the molar ratio of the starting substrate to the standard remained constant. The whole procedure was repeated for compound X using bibenzyl as the glpc standard. The result of the test in benzene was the same as that for epoxide V. In THF, two new materials were detected but not identified. The molar ratio of the starting substrate to the standard was about 10% of the ratio in the stock solution.

The interconversion of 1-phenyl- and 2-phenylethanols (III and IV respectively) in the presence of LAH and of aluminum hydride was tested. (a) An aliquot of freshly distilled compound III in benzene (0.43 mmole, 2 mL) was mixed with LAH (0.37 mmole). This mixture was allowed to stand at 61° for 16 h. Glpc analysis of the hydrolyzed sample revealed that no new material was obtained.
(b) Similarly, compound IV (0.53 mmole) was treated with LAH (0.41 mmole) in benzene (2 mL) in the same way. Glpc analysis of the hydrolyzed sample revealed that only the starting material was present. (c) Likewise, 2-phenylethanol (0.72 mmole) was mixed with LAH (0.50 mmole) in THF (2 mL) following the general procedure. Glpc analysis of the hydrolyzed sample revealed no other new signals on

the chromatogram. (d) Freshly distilled acetophenone (0.39 mmole) was mixed with LAH (0.35 mmole) in benzene (2 mL) at 61° and allowed to stand at this temperature for 16 h. The reaction mixture was worked up in the usual way with dilute sulfuric acid and dried over anhydrous magnesium sulfate. The mixture was analyzed by glpc and the product yields were quantified against an added standard p-di-tert-butylbenzene (0.11 mmole). Only 1-phenylethanol (80.0%) was detected along with the starting material (9.6%). (e) An aliquot (1 mL) of a stock THF solution containing 1-phenylethanol (0.31 M), 2-phenylethanol (0.24 M) and glpc standard p-di-tert-butylbenzene (0.039 M) was treated with a volume (1 mL) of a THF solution of aluminum hydride (hydride equivalence = 0.70 M), following the general procedure for the reaction with aluminum hydride in THF. Glpc analysis of the hydrolyzed mixture suggested that the molar ratio of either starting alcohol to the standard remained constant upon the treatment.

The isomerization of 1-cyclohexyl- and 2-cyclohexylethanols (VIII and IX respectively) in the presence of aluminum hydride was likewise tested (see (e) of preceding paragraph). Again, the molar ratio of either starting alcohol to the glpc standard (bibenzyl in this case) was the same as that before the treatment.

REFERENCES

1. The report was submitted before the Symposium on Hydrides and Related Compounds at the Chicago meeting of ACS on September 10, 1946. The subject of the report was published (Ref. (a)) together with two related papers.

   (a) Finholt, A.E.; Bond, A.C. Jr.; Schlesinger, H.I. J. Am. Chem. Soc. **1947**, 69, 1199.

   (b) Nystrom, R.F.; Brown, W.G. J. Am. Chem. Soc. **1947**, 69, 1197.

   (c) Nystrom, R.F.; Brown, W.G. J. Am. Chem. Soc. **1947**, 69, 2548.

2. Brown, H.C.; Yoon, M.N. J. Am. Chem. Soc. **1966**, 88, 1464.

3. (a) Paddock, N.L. Nature **1951**, 167, 1070.

   (b) Noth, H. Angew. Chem. **1961**, 73, 371.

   (c) Evans, G.G.; Kennedy, J.K.; DeGeco, F.P. J. Inorg. Nucl. Chem. **1957**, 4, 40.

   (d) Jarden, G.; Draffezyth, K. Z. Anorg. Allg. Chem. **1956**, 283, 27.

4. (a) Ashby, E.C.; Dobbs, F.R.; Hopkins, H.P. Jr. J. Am. Chem. Soc. **1973**, 95, 2823.

   (b) Alpatova, N.M.; Dymava, T.N.; Kessler, Y.M.; Osepov, O.R. Russ. Chem. Rev. **1968**, 37, 99.

5. Shirk, A.E.; Shriver, D.F. J. Am. Chem. Soc. **1973**, 95, 5904.

6. (a) Dautel, R.; Zeil, W. Z. Elektrochem. **1960**, 64, 1234.

   (b) Adiks, T.G.; Gavrilenko, V.V.; Zakharkin, I.; Ingat'eva, L.A. Zh. Prikl. Spektrosk. **1967**, 6, 806.

7. Lippincott, E.R. J. Chem. Phys. **1949**, 17, 1351.

8. (a) Wiberg, E.; Schmidt, M. Z. Naturforsch. **1951**, 6b, 333.

   (b) Wiberg, E.; Graf, H.; Schmidt, M.; Uson, R. Z. Naturforsch. **1952**, 7b, 578.

   (c) Wiberg, E.; Jahn, A. Z. Naturforsch. **1952**, 7b, 581.

9. Wiberg, E.; Goesele, W. Z. Naturforsch. **1956**, 11b, 485.

10. Gaylord, N.G. "Reduction with complex metal hydrides"; Interscience: New York, 1956.

11. Karrer, P. Angew. Chem. **1950**, 62, 334.

12. Bailey, W.J.; Marktscheffel, F. J. Org. Chem. **1960**, 25, 1797.

13. Yoon, M.N.; Brown, H.C. J. Am. Chem. Soc. **1968**, 90, 2927.

14. A survey of the types of functional groups effected by LAH and AlH_3 could be found in two recent review articles:
    (a) Brown, H.C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.
    (b) Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* **1979**, *12*, 3.
15. Exceptions were observed in benzyl ethers, allyl aryl and vinyl allyl ethers, and various epoxides. See:
    (a) Klabunovskii, E.I. *Russ. Chem. Rev.* **1966**, *35*, 546.
    (b) Tweedie, V.L.; Cuscurida, M. *J. Am. Chem. Soc.* **1957**, *79*, 5463.
    (c) Tweedie, V.L.; Barrow, B.G. *J. Org. Chem.* **1960**, *25*, 2023.
16. Carbon-carbon double bonds conjugated with C=O bond can be hydrogenated by LAH, for examples, cinnamic acid, see ref. 1(c); and allylic alcohols, see:
    (a) Synder, E.I. *J. Org. Chem.* **1967**, *32*, 3531;
    (b) Bordon, W.T. *J. Am. Chem. Soc.* **1968**, *90*, 2197.
17. Trevoy, L.W.; Brown, W.G. *J. Am. Chem. Soc.* **1947**, *69*, 1197.
18. Lemaine, A.; Rassat, A.; Ranet, J-P. *Tetrahedron Lett.* **1964**, 3507.

19. Vail, O.R.; Wheeler, D.M.S. J. Org. Chem. **1962**, 27, 3803.

20. House, H.O. "Modern Synthetic Reactions"; W.A. Benjamin: Menlo Park, 1972, p. 45.

21. Ashby, E.C.; Boone, J.R. J. Am. Chem. Soc. **1976**, 98, 5524.

22. Wiegers, K.E.; Smith, S.G. J. Am. Chem. Soc. **1977**, 99, 1480; Wiegers, K.E. Diss. Abs. Int. **1977**, 37, 4822B.

23. (a) Noyce, D.S.; Denney, D.B. J. Am. Chem. Soc. **1950**, 72, 5743.

    (b) Brown, H.C.; Muzzio, J. J. Am. Chem. Soc. **1966**, 88, 2811.

24. Brown, H.C.; Varma, V. J. Am. Chem. Soc. **1966**, 88, 2870.

25. (a) Dauben, W.G.; Fonken, G.J.; Noyce, D.S. J. Am. Chem. Soc., **1956**, 78, 2579.

    (b) Brown, H.C.; Deck, H. J. Am. Chem. Soc., **1965**, 87, 5620.

26. (a) Cherest, M.; Felkin, H.; Prudent, N. Tetrahedron Lett. **1968**, 2199.

    (b) Cherest, M.; Felkin, H. Tetrahedron Lett. **1968**, 2205.

    (c) Wipke, W.T.; Gund, P. J. Am. Chem. Soc. **1976**, 98, 8107.

27. Rei, M.H. J. Org. Chem. **1979**, 44, 2760.

28. (a) Ayres, D.C.; Sawdaye, R. J. Chem. Soc. B **1967**, 581.

(b) Ayres, D.C.; Kirk, D.N.; Sawdaye, R. J. Chem. Soc. B **1970**, 505.

(c) Ayres, D.C.; Kirk, D.N.; Sawdaye, R. J. Chem. Soc. B **1970**, 1133.

29. Murphy, D.K.; Alumbaugh, R.L.; Rickborn, B. J. Am. Chem. Soc. **1969**, 91, 2649.

30. (a) Rickborn, B.; Quartucci, J. J. Org. Chem. **1964**, 29, 3185.

(b) Rickborn, B.; Luo, S-Y. J. Org. Chem. **1965**, 30, 2212.

31. Schwab, J.M. J. Org. Chem. **1983**, 48, 2105.

32. Eliel, E.L. In "Steric effects in organic chemistry"; Newman, M.S., Ed.; John Wiley and Sons: New York, 1956, p. 106.

33. Parker, R.E.; Isaacs, N.S. Chem. Rev. **1959**, 59, 737.

34. Fuchs, R.; Vander Werf, C.A. J. Am. Chem. Soc. **1952**, 74, 5917.

35. Eliel, E.L.; Rerick, M.N. J. Am. Chem. Soc. **1960**, 82, 1362.

36. Elenbaumer, R.L.; Mosher, H.S.; Morrison, J.D.; Tomaszewski, J.E. J. Org. Chem. **1981**, 46, 4034.

37. Ashby, E.C.; Prather, J. J. Am. Chem. Soc. **1966**, 88, 729.

38. Eliel, E.L.; Delmonte, D.W. J. Am. Chem. Soc. **1958**, 80, 1744.

39. Rerick, M.N.; Eliel, E.L. J. Am. Chem. Soc. **1962**, 84, 2356.

40. Rerick, N.N. In "Reduction"; Augustine, R.L., Ed.; Marcel Dekker: New York, 1968, p. 1.

41. Ashby, E.C.; Cooke, B. J. Am. Chem. Soc. **1968**, 90, 1625.

42. Sankawa, U.; Sato, T. Tetrahedron Lett. **1978**, 981.

43. (a) Lansbury, P.T.; Pattison, V.A. Tetrahedron Lett. **1966**, 3073.
    (b) Lansbury, P.T.; Scharf, D.J.; Pattison, V.A. J. Org. Chem. **1967**, 32, 1748.

44. (a) Laurent, E.; Villa, P. Bull. Soc. Chim. Fr. **1969**, 249.
    (b) Guyon, R.; Villa, P. Bull. Soc. Chim. Fr. **1972**, 1375.
    (c) Guyon, R.; Villa, P. Bull. Soc. Chim. Fr. **1975**, 2599.

45. Cooke, B.; Ashby, E.C.; Lott, J. J. Org. Chem. **1968**, 33, 1132.

46. Eliel, E.L. J. Am. Chem. Soc. **1949**, 71, 3970.

47. Mousseron, M.; Jacquier, R.; Mousseron-Canet, M.; Zagdoun, R. Bull. Soc. Chim. Fr. **1952**, 1043.

48. Helmkamp, G.K.; Rickborn, R.F. J. Org. Chem. **1957**, 22, 479.

49. Alexander, E.R. J. Am. Chem. Soc. **1950**, 72, 3796.

50. Johnson, J.E.; Blizzard, R.H.; Carhart, H.W. J. Am. Chem. Soc. **1948**, 70, 3664.

51. Krishnamurthy, S.; Brown, H.C. J. Org. Chem. **1980**, 45, 849.

52. Malter, D.J.; Wotiz, J.H.; Hollingsworth, C.A. J. Am. Chem. Soc. **1956**, 78, 1311.

53. Eliel, E.L.; Traxler, J.T. J. Am. Chem. Soc. **1956**, 78, 4049.

54. Karabatsos, G.J.; Stone, R.L. J. Org. Chem. **1968**, 33, 619.

55. (a) Alsop, D.J.; Burdon, J.; Tatlov, J.C. J. Chem. Soc. **1962**, 1801.
    (b) Karpov, V.M.; Platonov, V.E.; Yakobson, G.G. Izu. Sib. Otd. Aka. Nauk. SSSR Ser. Khim. Nauk **1972**, 6, 88.

56. Brown, H.C.; Krishnamurthy, S. J. Org. Chem. **1969**, 34, 3918.

57. (a) Bunnett, J.F. Q. Rev. Chem. Soc. **1958**, 12, 1.
    (b) Bunnett, J.F.; Zahler, R.E. Chem. Rev. **1951**, 49, 273.

58. Chung, S.; Chung, F. *Tetrahedron Lett.* **1979**, 2473.

59. Barltrop, J.A.; Bradbury, D. *J. Am. Chem. Soc.* **1973**, *95*, 5085.

60. Ashby, E.C.; DePriest, R.N.; Goel, A.B.; Wenderoth, B.; Pham, T.N. *J. Org. Chem.* **1984**, *49*, 3545.

61. Chung, S.; Filmore, K.L. *J. Chem. Soc. Chem. Comm.* **1983**, 358.

62. Singh, P.R.; Nigam, A.; Khurana, J.M. *Tetrahedron Lett.* **1980**, 4753.

63. Chung, S.K. *J. Org. Chem.* **1980**, *45*, 3513.

64. Singh, P.R.; Khurana, J.M.; Nigam, A. *Tetrahedron Lett.* **1981**, 2901.

65. (a) Ziegler, E.; Klementschitz, W. *Monatsh.* **1950**, *81*, 113.

    (b) See ref. 81 .

66. The estimations have been derived from ESR measurements (Ref. (a)) and MINDO calculations (Ref. (b)):

    (a) Fessenden, R.W.; Schuler, R.H. *J. Chem. Phys.* **1963**, *39*, 2147.

    (b) Kasai, P.H.; Whipple, E.B. *J. Am. Chem. Soc.* **1967**, *89*, 1033.

    (c) Dewar, M.J.S.; Shanshal, M. *J. Am. Chem. Soc.* **1969**, *91*, 3654.

67. Brown, H.C.; Fletcher, R.S.; Johannesen, R.B. *J. Am. Chem. Soc.* **1951**, *73*, 212.

68. Yamanaka, H.; Yagi, T.; Teramura, K.; Ando, T. *Chem. Comm.* **1971**, 380.

69. Hatem, J.; Waegell, B. *Tetrahedron Lett.* **1973**, 2023.

70. Jefford, C.W.; Kirkpatrick, D.; Delay, F. *J. Am. Chem. Soc.* **1972**, *94*, 8905.

71. Jefford, C.W.; Burger, U.; Laffer, M.H.; Kabengele, T. *Tetrahedron Lett.* **1973**, 2483.

72. 1-Bromoadamantane and 1-bromotriptycene have been reported to be converted to the corresponding hydrocarbons in good yield by LAH. See:

    (a) Bingham, R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1971**, *93*, 3189.

    (b) Jefford, C.W.; McCreadie, R.; Muller, P.; Siegfried, [illegible] *J. Chem. Educ.* **1971**, *48*, 708.

73. Shimizu, N.; [illegible]anabe, K.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **198**[illegible], 885.

74. Groves, J.T.; Ma, K.W. *J. Am. Chem. Soc.* **1974**, *96*, 6527.

75. Seyferth, D.; Yamazaki, H.; Alleston, D.L. *J. Org. Chem.* **1963**, *28*, 703.

76. Seyferth, D.; Prokai, B. *J. Org. Chem.* **1966**, *31*, 1702.

77. Osborn, C.L.; Shields, T.G.; Shoulders, B.A.; Cardenas, C.G.; Gardner, P.D. Chem. Ind. (London) **1965**, 766.

78. Kuivila, H.G. Acc. Chem. Res. **1968**, 1, 299.

79. Hatem, J.; Waegell, B. Tetrahedron Lett. **1981**, 2019.

80. Ando, T.; Namigata, F.; Yamanaka, H.; Funasaka, W. J. Am. Chem. Soc. **1967**, 89, 5719.

81. For the comparative studies of bicyclo[3.2.1]octenyl dihalides by LAH and tri-n-butyltin hydride, see Jefford, C.W.; Sweeney, A.; Delay, F. Helv. Chim. Acta **1972**, 55, 2214.

82. Barnett, W.E.; Koebel, R.F. Chem. Comm. **1969**, 875.

83. Dibeler, V.H. J. Res. Natl. Bur. Standards **1950**, 44, 363.

84. Kupchik, E.J.; Kiesel, R.J. J. Org. Chem. **1964**, 29, 764.

85. Blackburn, E.V.; Tanner, D.D. J. Am. Chem. Soc. **1980**, 102, 692.

86. Tamblyn, W.H.; Vogler, E.A.; Kochi, J.K. J. Org. Chem. **1980**, 45, 3912.

87. Carlsson, D.J.; Ingold, K.U. J. Am. Chem. Soc. **1968**, 90, 1055, 7047.

88. Grady, G.L.; Danlyiw, T.J.; Rabideaux, P. J. Organomet. Chem. **1977**, 142, 67.

89. Kuivila, H.G.; Menapace, L.W.; Warner, C.R. J. Am. Chem. Soc. **1962**, 82, 3584.

90. Kuivila, H.G. In "Organotin Compounds: New Chemistry and Applications", Advances in Chem. Series No. 157; Zuckerman, J.J., Ed.; A.C.S.: Washington, 1976, p. 41.

91. Kochi, J.K. "Organometallic Mechanisms and Catalysis"; Academic Press: New York, 1978.

92. Kuivila, H.G. Synthesis **1970**, 2, 499.

93. Neumann, W.P.; Heymann, E. Justus Liebigs Ann. Chem **1965**, 683, 11.

94. (a) Pereyre, M.; Valade, J. C.R. Acad. Sci. Paris **1965**, 258, 4785; 260, 581.

(b) Pereyre, M.; Godet, J.Y. Tetrahedron Lett. **1970**, 3653.

(c) Godet, J.Y.; Pereyre, M. C.R. Acad. Sci. Paris **1973**, 277, 211.

95. Diaz, G.E. Ph.D. Thesis **1983**, University of Alberta.

96. (a) Blick, F.F.; Powers, L.D. J. Am. Chem. Soc. **1929**, 51, 3378.

(b) Holms, T.; Crossland, I. Acta Chem. Scand. **1971**, 25, 59.

(c) Holms, T.; Crossland, I. Acta Chem. Scand. Ser. B **1979**, 33, 421.

(d) Ashby, E.C. Pure Appl. Chem. **1980**, 52, 545.

97. For LAH reaction, see Karrer, P.; Ruttner, O. Helv. Chim. Acta **1950**, 33, 812.
For Grignard reaction, see Kharasch, M.S.; Urry, W.H. J. Org. Chem. **1948**, 13, 101.

98. For LAH reaction, see ref. 119(a).
For Grignard reaction, see Karrer, P. Bull. Soc. Chim. Fr. **1950**, 907.

99. Razuvaev, G.A.; Abakumov, G.A.; Klimov, E.S.; Glayshev, E.W.; Bayushkin, P.Y. Izu. Akad. Nauk. SSSR Ser. Khim (Eng. Transl.) **1977**, 26, 1034.

100. (a) Brown, H.C.; Midland, M.M. Angew. Chim. Int. Ed. Engl. **1972**, 11, 692.
(b) Brown, H.C.; Kabalka, G.W. J. Am. Chem. Soc. **1970**, 92, 712, 714.
(c) Miyaura, N.; Harada, M.; Itoh, M.; Suzuki, A. Chem. Lett. **1973**, 1145.

101. Kabalka, G.W.; Daley, R.F. J. Am. Chem. Soc. **1973**, 95, 4428.

102. Kaim, W. J. Organomet. Chem. **1981**, 215, 325, 337.

103. Klinger, R.J.; Mochida, K.; Kochi, J.K. J. Am. Chem. Soc. **1979**, 101, 6626.

104. (a) Whitesides, G.M.; San Filippo, J. Jr. J. Am. Chem. Soc. **1970**, 92, 6611.
(b) See also Bartlett, P.D.; Fickes, G.N.; Haupt, F.C.; Helgesen, R. Acc. Chem. Res. **1970**, 3, 177.

105. (a) Streitwieser, A. Jr. "Solvolytic Displacement Reactions"; McGraw-Hill: New York, 1962.

(b) Brown, H.C.; Krishnamurthy, S.; Coleman, R.A. *J. Am. Chem. Soc.* **1972**, *94*, 1750.

106. (a) Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* **1983**, *48*, 3085, 3091.

(b) Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

107. Ashby, E.C.; Wenderoth, B.; Pham, T.N.; Park, W-S. *J. Org. Chem.* **1984**, *49*, 4505.

108. Ashby, E.C.; DePriest, R.N.; Pham, T.N. *Tetrahedron Lett.* **1983**, 2825.

109. Ashby, E.C.; Goel, A.B.; DePriest, R.N.; *Tetrahedron Lett.* **1981**, 3729.

110. Ashby, E.C.; DePriest, R.N.; Goel, A.B. *Tetrahedron Lett.* **1981**, 1763.

111. Ashby, E.C.; Goel, A.B. *J. Org. Chem.* **1981**, *46*, 3934.

112. Ashby, E.C.; Goel, A.B. *J. Am. Chem. Soc.* **1980**, *102*, 7779.

113. Ashby, E.C.; Goel, A.B.; Argyropoulos, J.N. *Tetrahedron Lett.* **1982**, 2273.

114. Ashby, E.C.; Goel, A.B.; DePriest, R.N. *Tetrahedron Lett.* **1981**, 4355.

115. Ashby, E.C.; Goel, A.B. *Tetrahedron Lett.* **1981**, 1879.

116. Ashby, E.C.; Goel, A.B.; DePriest, R.N.; Prasad, H.S. *J. Am. Chem. Soc.* **1981**, *103*, 973.

117. Wang, S.S.; Sukenik, C.N. *J. Org. Chem.* **1985**, *50*, 653.

118. (a) Schmidt, H.; Karrer, P. *Helv. Chim. Acta* **1949**, *32*, 1371.

(b) Corey, E.J.; Howell, M.G.; Boston, A.; Young, R.L.; Sneen, R.A. *J. Am. Chem. Soc.* **1956**, *78*, 5036.

(c) Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* **1967** *89*, 4008.

(d) Kraus, W.; Chassin, C. *Tetrahedron Lett.* **1970**, 1443.

(e) Cram, D.J. *J. Am. Chem. Soc.* **1952**, *74*, 2149.

119. (a) Story, P.R.; Saunders, M. *J. Am. Chem. Soc.* **1962**, *84*, 4876.

(b) Paquette, L.A.; Storm, P.C. *J. Org. Chem.* **1970**, *35*, 3390.

120. Solvent effects on the reactions of halides and tosylates with LAH: Krishnamurthy, S. *J. Org. Chem.* **1980**, *46*, 2550; see also ref. 117.

121. Kumar, K.; Wang, S.S.; Sukenik, C.N. *J. Org. Chem.* **1984**, *49*, 665.

122. Lansbury, P.T.; Peterson, J.O. J. Am. Chem. Soc. **1961**, 83, 3537; **1963**, 85, 2236.

123. Gause, E.M.; Rowlands, J.R. Spectrsoc. Lett. **1976**, 9, 219.

124. Kaim, W. Angew. Chem. Int. Ed. Engl. **1982**, 21, 141; Angew. Chem. Suppl. **1982**, 298-304.

125. Carrington, A.; Dravnieks, F.; Symons, M.C.R. J. Chem. Soc. **1959**, 947.

126. Michaud, P.; Astruc, D.; Ammeter, J.M. J. Am. Chem. Soc. **1982**, 104, 3753.

127. Nesmeyanov, A.N.; Solodovmikov, S.P.; Vol'kenau, N.A.; Kotova, L.S.; Sinitsyna, N.A. J. Organomet. Chem. **1978**, 148, C5.

128. Tanner, D.D.; Diaz, G.E.; Potter, A. J. Org. Chem. **1985**, 50, 2149.

129. Bergmann, F.; Kalmus, A. J. Am. Chem. Soc. **1954**, 76, 4137.

130. Ershov, V.V.; Volod'kin, A.A.; Portnykh, N.V. Bull. Acad. Sci. USSR **1966**, 1632; **1967**, 1352.

131. (a) Schartz, L.H.; Flor, R.V. Chem. Comm. **1968**, 1129.

(b) Schartz, L.H.; Flor, R.V. J. Org. Chem. **1969**, 34, 1499.

132. Zakharkin, L.I.; Maslin, D.N.; Gavrilenko, V.V. Izv. Akad. Nauk. SSR Ser. Khim. **1964**, 561.

133. (a) Jorgensen, M.J.; Friend, A.W. J. Am. Chem. Soc. **1965**, 87, 1815.

(b) Vyeda, R.T.; Cram, D.J. J. Org. Chem. **1965**, 30, 2083.

134. Brown, H.C.; Weissman, P.M.; Yoon, M.N. J. Am. Chem. Soc. **1966**, 88, 1458.

135. Higuchi, T. Anal. Chem. **1950**, 22, 955.

136. Truce, W.E.; Sack, B.H. J. Am. Chem. Soc. **1948**, 70, 3959.

137. Parker, R.E. Adv. Fluorine Chem. **1963**, 3, 63.

138. (a) Calloway, N.O. J. Am. Chem. Soc. **1937**, 59, 1474.

(b) Olah, G.A.; Kuhn, S.J. J. Org. Chem. **1964**, 29, 2317.

139. Paleta, O. Fluorine Chem. Rev. **1977**, 8, 39.

140. The bond dissociation energy of C-F in fluoromethane was quoted in ref. 139 to be 422 kJ mol^{-1}, whereas that of Al-F in aluminum trifluoride, 615 kJ mol^{-1}. This represents a difference of 193 kJ mol^{-1}, compared to 138 and 133 kJ mol^{-1} associated with those of Cl and Br bonds respectively.

141. Papanastassiou, Z.B.; Bruno, R.J. J. Org. Chem. **1964**, 29, 2870.

142. Pattison, F.L.M.; Howell, W.C.; White, R.W. J. Am. Chem. Soc. **1956**, 78, 3487.

143. (a) Eliel, E.L.; Prossman, T.J. J. Am. Chem. Soc. **1956**, 78, 4045.

(b) Eliel, E.L.; Freeman, J.P. J. Am. Chem. Soc. **1952**, 74, 923.

(c) Eliel, E.L. Res. Chem. Progr. **1961**, 22, 129.

144. DeKimpe, N.; DeBuyck, L.; Verhe, R.; Schamp, N. Tetrahedron **1984**, 40, 3291.

145. March, J. "Advanced Organic Chemistry", 2nd Ed.; McGraw Hill: New York; **1977**, p. 969.

146. "Handbook of Chemistry and Physics", 64th Ed., Weast, R.C., Ed.; Chemical Rubber Company Press: Cleveland, 1983, p. C-107.

147. Aldrich Catalog Handbook of Fine Chemicals, 1982-1983.

148. Buckle, F.J.; Heap, R.; Saunders, B.C. J. Chem. Soc. **1949**, 912.

149. Gryszkiewicz-Trochimoski, M.M.E.; Sporzynski, A.; Wnuk, J. Rec. Trav. Chem. **1947**, 66, 419.

150. Bergmann, E.D.; Cohen, S.; Hoffman, E.; Randmeir, Z. J. Chem. Soc. **1961**, 3452.

151. Leroy, J. J. Org. Chem. **1981**, 46, 206.

152. Drake, N.L.; Cooke, G.B. Org. Syntheses **1943**, II, 406.

153. Dreger, E.E. Org. Synthesis **1941**, I, 306.

154. Warnhoff, E.W.; Martin, D.G.; Johnson, W.S. Org. Syntheses **1963**, IV, 162.

155. Bare, T.M.; House, H.O. Org. Syntheses **1973**, V, 775.

156. Paquette, L.A.; Barrett, J.H. Org. Syntheses **1973**, V, 467.

157. Chirko, A.I.; Ivanov, K.I.; Tishchenko, I.G.; Sosnovskii, G.M. J. Org. Chem. USSR Engl. Transl. **1975**, 11, 2091.

158. Vogel, A.I. "A Textbook of Practical Organic Chemistry", 3rd Ed.; Longman: London, 1956, p. 173.