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THE STRUCTURES AND REACTIVITIES OF SEVERAL MAIN-GROUP ORGANOMETALLICS: THEIR REACTIONS BY HETEROLYTIC AND/OR HOMOLYTIC PROCESSES.

BY 

CHI-MING YANG

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF THE DOCTOR OF PHILOSOPHY.

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To my parents and my wife, yuhong

ABSTRACT

The single electron transfer (SET) reactions of some main-group organometallics are investigated. The structure and mechanism of formation of an inorganic NADH model, lithium tetrakis(N-dihydropyridyl)aluminate (LDPA), was determined. Five LDPA isomers are reversibly formed. The isomers contain both 1,2- and 1,4-dihydropyridyl ligands. The stepwise addition of ligands to form LDPA can be observed (^{27}Al NMR). Five aluminate species are detectable: LAH, mono-, di- and tri(dihydropyridyl)aluminum hydride and LDPA. The hydrolysis of LDPA yields a mixture of 1,4-, 1,2-, and 2,5-dihydropyridines (DHP).

The reactions of a series of chemical probes, mesityl phenyl ketone (MPK), dimesityl ketone (DMK), bromophenyl ketones, 2,6-di-*t*-butylbenzoquinone, bromotriphenylmethane, and 6-halo-1-hexene (halo = I, Br) were employed in order to determine whether a SET mechanism is involved in the reactions of LDPA. The observation that ketyl radicals were formed during the reduction of the aromatic ketones and that the radicals formed from the fragmentation of the substrate ketyls were trapped with an electrophile established that during the LDPA reduction (*i.e.*, dehalogenation) of ketones and alkyl halides both polar and SET processes are involved and that hydride transfer is the predominant reaction; however, when the polar process is sterically blocked, or when the substrate is a good electron acceptor, SET should become more important.

The reductions of a number of mechanistic probes with several borate complexes, $NaBH_4$, $Na(C_2H_5)_3BH$, and lithium dimesityl borohydride have been shown to proceed by both a SET-hydrogen atom abstraction

mechanism and by a hydride transfer process. Only when the reducing agent and/or the substrate is sterically hindered or when the acceptor is a strong oxidizing agent is the homolytic pathway preferred.

The fragmentation probes, bromophenyl ketones, were used to study the mechanism of the reactions of a number of Grignard reagents (RMgCl, R = *t*-Bu, *n*-Bu, Me, Phenyl, and Allyl). Several criteria: ketyl formation and fragmentation, aromatic alkylation, and products diagnostic of radical reactions were used to establish that SET reaction pathways are involved in the formation of the products. There is no indication that a SET process is involved in the reactions of the allylic Grignard reagent with these probes.

The base catalyzed condensation of a 1:1 mixture of 1,2- and 2,5-DHP's, carried out in the presence of oxygen, affords a 89% yield of (±)-anatabine. Using deuterium labelled reactants the mechanism for the formation of (±)-anatabine was shown to be consistent with the generally accepted, although unsubstantiated, biosynthetic pathway.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

The following abbreviations are used throughout the thesis:

AIBN	α, α'-azobis-*iso*-butyronitrile, $(CH_3)_2C(CN)$-N=N-$C(CN)(CH_3)_2$; a free radical initiator and used to initiate the free radical chain reactions.
AN	acetonitrile
APT	attached proton test
Ar	aryl
BPMK	bromophenyl mesityl ketone
BPO	di-*tert*-butylperoxide, $(CH_3)_3COOC(CH_3)_3$; a free radical initiator
n-Bu	*n*-butyl
i-Bu	*iso*-butyl
t-Bu	*tert*-butyl
CIDNP	chemically induced dynamic nuclear polarization
δ	NMR chemical shift
d	day
DCPH	dicyclohexylphosphine, $(c\text{-}C_6H_{11})_2PH$; a hydrogen atom donor
DHP	dihydropyridine
DMF	N, N-dimethylformamide
DMK	dimesityl ketone

DNB	*m*- or *p*-dinitrobenzene, $C_6H_4(NO_2)_2$; a strong electron acceptor and used to inhibit single electron transfer chain reactions
EPR	electron paramagnetic resonance
eq	equation
Et	ethyl
Fig.	Figure
g	gyromagnetic ratio
G	gauss
GC	gas phase chromatograph
h	hour
HRMS	high resolution mass spectroscopy
IR	infrared spectroscopy
LAD	lithium aluminum deuteride, $LiAlD_4$
LAH	lithium aluminum hydride, $LiAlH_4$
LDPA	lithium tetrakis(N-dihydropyridyl)aluminate
m	*meta*
Me	methyl
Mes	mesityl
MPK	mesityl phenyl ketone
MS	mass spectroscopy
min	minutes
NAD(NADH)	nicotinamide adenine dinucleotide (reduced form)
NADPH	nicotinamide adenine dinucleotide phosphate
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect

o	*ortho*
p	*para*
Ph	phenyl
n-Pr	*n*-propyl
i-Pr	*iso*-propyl
Py	pyridine
r t	room temperature
SET	single electron transfer
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet absorption spectroscopy
ν	wave number

CHAPTER 1

The Single Electron Transfer (SET) Reactions of Some Main-Group Organometallics

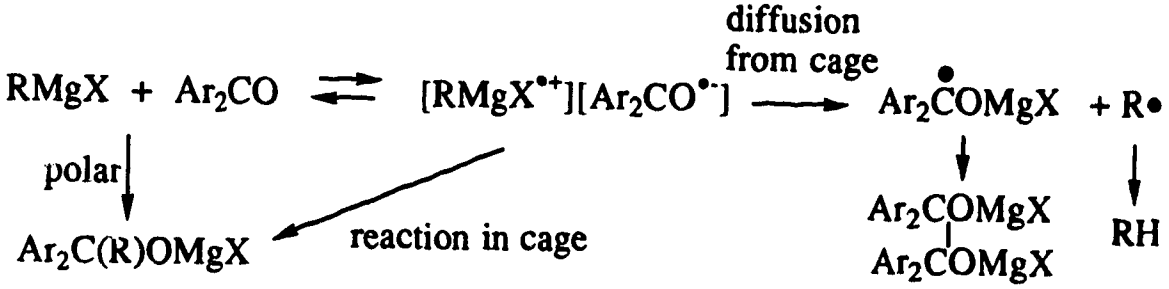
I-1. A Brief History of The Single Electron Transfer (SET) Reactions of Main-Group Organometallics in Organic Chemistry

Single electron transfer (SET or ET)[1] is an exchange of a *single* electron between molecules. In 1916 Schlenk[2a] first suggested that electron transfer from a diamagnetic carbanion, Ph_3CNa, to an aromatic ketone, produced a highly colored intermediate, a ketyl. On dimerization the ketyl produced, after hydrolysis, the pinacol. The subsequent report that several Grignard reagents, RMgX, reduced Ph_2CO to pinacol or benzhydrol received considerable attention.[2b-e]

Single electron transfer reactions involving main-group organometallics is a major area[3] in the research field of SET reactions. Since most organometallics, including hydrides, are electron rich and can be used as reductants, SET may occur with suitable acceptors. The SET process can often be theoretically modeled using the Marcus equation.[4] Product analysis, and spectroscopic methods such as high-resolution electron paramagnetic resonance (EPR),[5] chemically induced dynamic nuclear polarization (CIDNP)[6] and electron nuclear double resonance (ENDOR)[7] make it possible to relate SET reactions with the structure and properties of the reactants. Some pioneering work was reported by Russell, Janzen, and Storm, on the electron transfer processes between carbanion and nitroanions, as SET reductants, with acceptor molecules such as nitroaromatics, azobenzene, and diarylketones.[5a] The use of lithium organocuprate additions as models for SET processes was studied by House in the 1960's.[8] Recently it was emphasized again by Ashby in the 1980's that the SET process is a major reaction pathway in organic chemistry.[9]

However, the relationship between the structural properties of the reactants and the nature and the proper identity of the radical intermediates has not always been established clearly.

Grignard reagent (RMgX) is one of the most important main-group organometallic in organic chemistry. The determination of oxidation potentials of RMgX is difficult, involving totally irreversible electrochemical processes.[10, 11] Ashby and co-workers[12] suggested in the early 1980's that the reaction of MeMgBr with 2-methylbenzophenone involved a radical intermediate (EPR) (Scheme I-1), and they subsequently tested this hypothesis further by using a cyclizable radical probe (5-hexenyl radical) that resulted in the formation of cyclized product as well as straight-chain product.[13] Holm, using a Hammett correlation, concurred with this suggestion.[14]

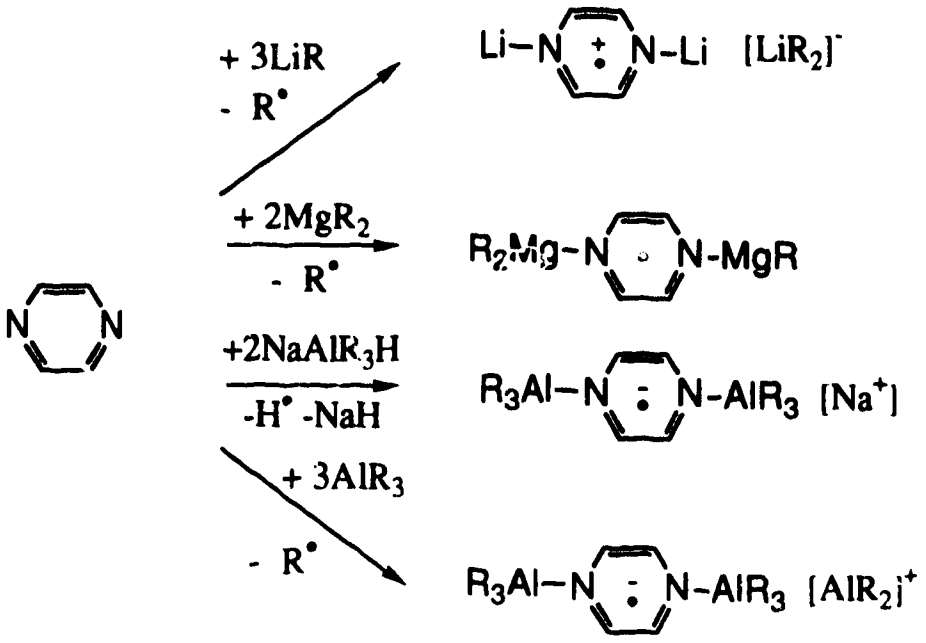


Scheme I-1

Evidence showing the broad relationship between polar and SET reactions with respect to the structure of the Grignard reagent and the ketone came from a relative rate study.[15] The results showed that with a

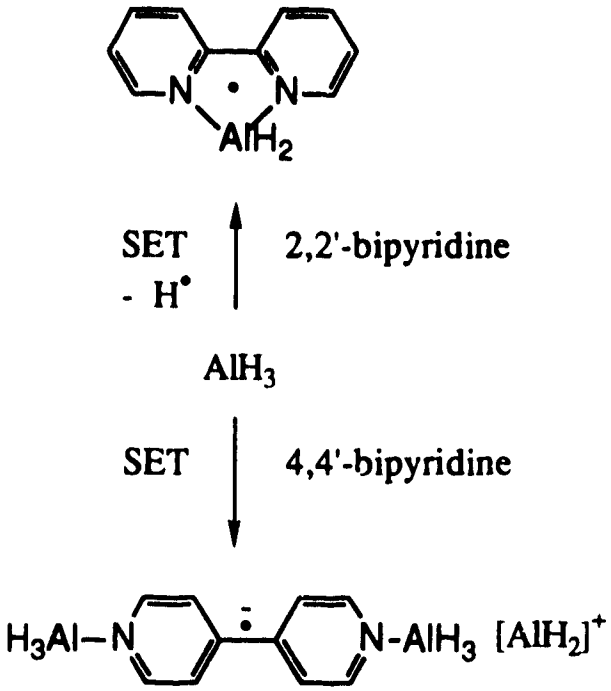
ketone that is difficult to reduce (such as acetone), the order of Grignard reaction rates is related to the structure, Me > Et > *i*-Pr > *t*-Bu, as would be expected for a polar reaction. However, when the ketone is easily reduced (*i.e.*, aromatic ketones) an electron transfer process takes place, and the order of the rates, with benzophenone, is the opposite, *i.e.*, *t*-Bu > *i*-Pr > Et > Me. These results were never published but only appeared in reviews.[11,15] It is shown that the mechanistic pathway (polar or SET) depends both on the structure of the ketone (*i.e.*, reduction potential) and the structure of the Grignard regent (*i.e.*, oxidation potential). SET is favored by 3° over 1° Grignard reagents and by ketones which are easily reduced.

It has been reported that the reactions of lithium alkyls proceed by two alternative pathways, a polar one and SET.[16] Kaim carried out some EPR-monitored single electron transfer experiments on the reactions of N-heterocycles with lithium reagents (alkyls),[17] magnesium reagents (diorganomagnesium compounds, MgR_2),[18] aluminum alkyls (AlR_3),[19] and alkyl aluminates.[20] A series of radical anions and/or radical cations was observed (Scheme I-2).



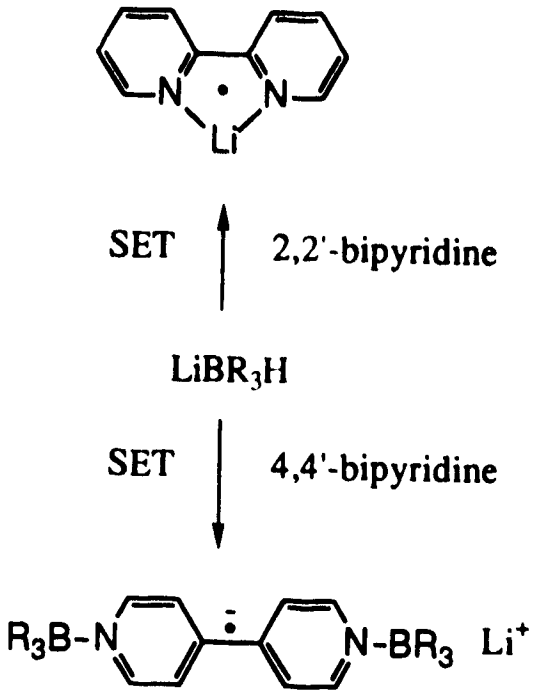
Scheme I-2

It was found that the chelate arrangement facilitates electron transfer and determines the composition of the organometallic radical complexes formed (Scheme I-3).[21]



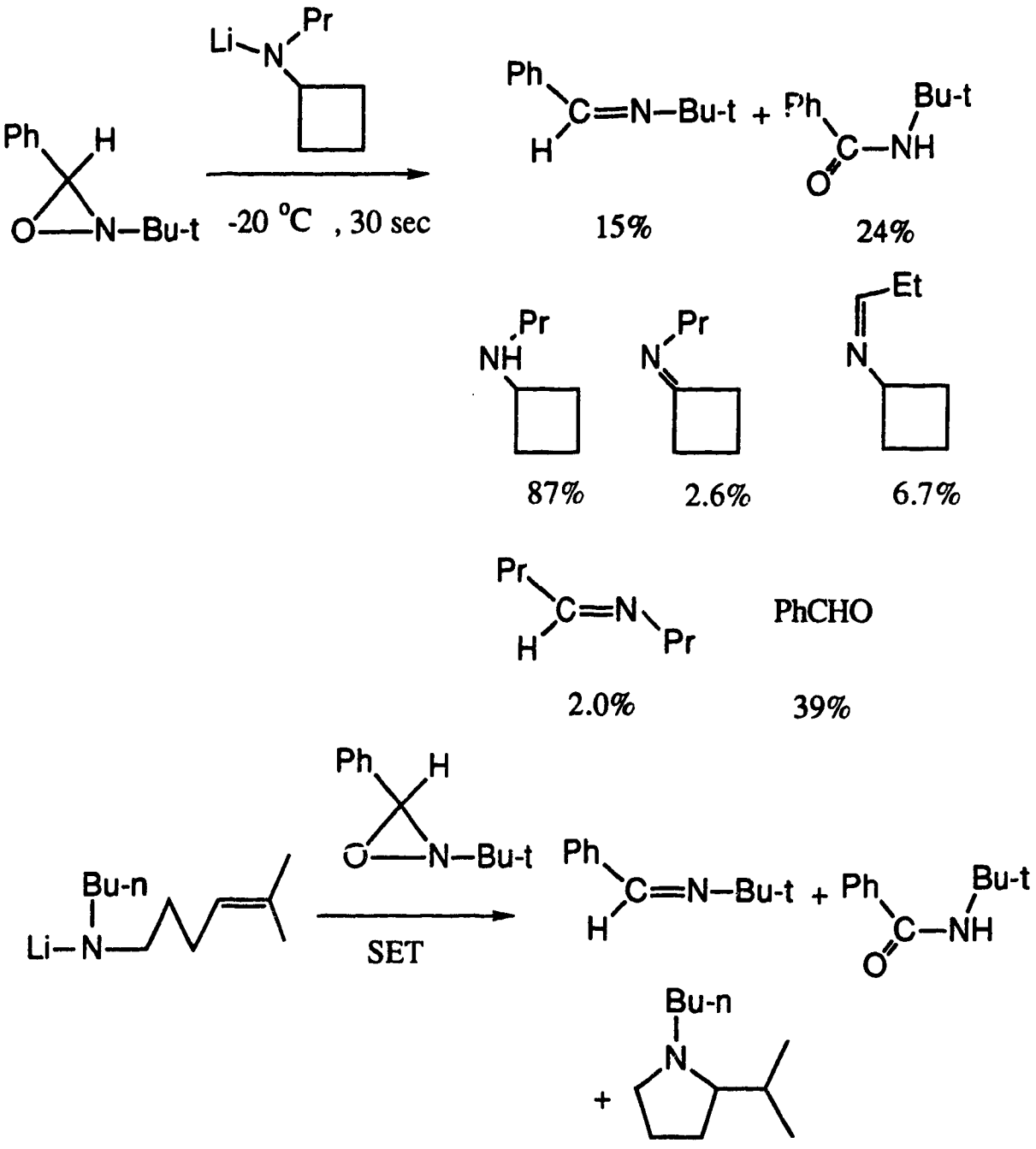
Scheme I-3

Electron transfer from borohydrides MBR_3H (M = Li, Na, K) to unsaturated N-heterocycles has recently been observed.[22] It seems that coordination equilibria also determine the structure of the radical complexes formed (Scheme I-4).[22]



Scheme I-4

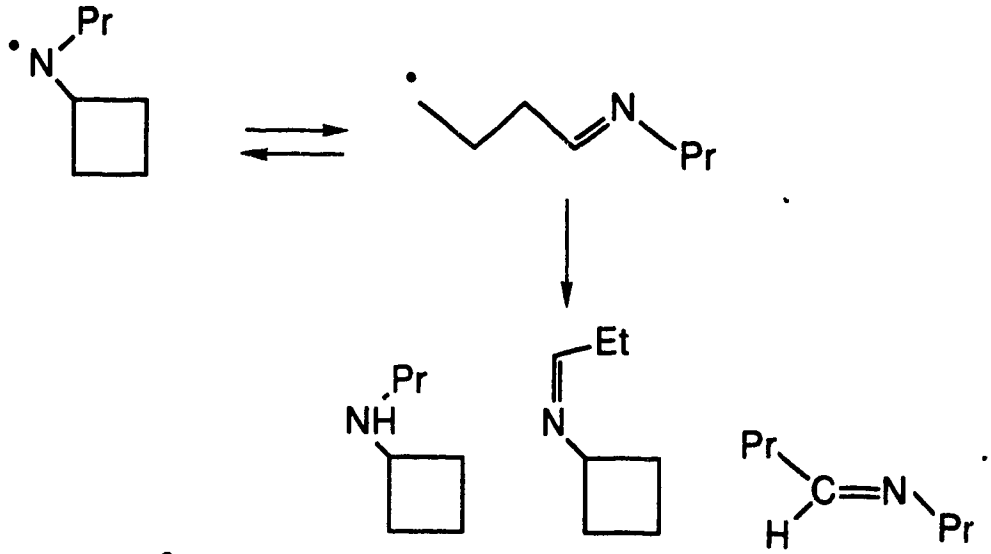
SET processes between oxaziridines and lithium dialkylamide have been reported by Newcomb.[23] The ring opened products from the N-cyclobutyl-propyl-aminyl radical were observed either from a reaction of N-lithio-N-cyclobutyl-propylamine with strong oxidant oxaziridines, or from a reaction of N-lithio-N-cyclobutyl-propylamine with the thianthrene radical cation (Scheme I-5)[23].


Li–N–Pr
Ph
H
O—N–Bu-t
-20 °C , 30 sec
Ph
C=N–Bu-t
H
+
Ph
Bu-t
C–NH
O
15%
24%
NH–Pr
N–Pr
N–Et
87%
2.6%
6.7%
Pr
C=N
H
Pr
PhCHO
2.0%
39%
Ph
H
O—N–Bu-t
Bu-n
Li–N
SET
Ph
C=N–Bu-t
H
+
Ph
Bu-t
C–NH
O
Bu-n
N
+

Scheme I-5

The cyclization of the N-butyl-5-methyl-1-hex-4-enaminyl radical was observed during the reaction of N-lithio-N-butyl-5-methyl-1-hex-4-enamine with the thianthrene radical cation (Scheme I-5).[24]

The independently generated N-cyclobutyl-propyl-aminyl radical was found to give products according to the following equation in Scheme I-6.[25]



At 135 °C:	0%	0%	48%
At 25 °C:	9%	0.4%	29%

Scheme I-6

Ashby suggested a SET mechanism for the reaction of lithium amides ($LiNR_2$) with aromatic ketones (EPR).[26] Although Marcus treatment does not exclude a radical pathway in the $LiNR_2$ reduction of Ph_2CO,[27] it is probably excluded by the observation that the reduction of Ph_2CO by N-lithio-N-butyl-5-methyl-1-hex-4-enamine yields Ph_2CHOH, but no cyclic

amine is obtained. It was concluded that the formation of benzophenone ketyl was actually due to a dianion of benzhydrol.[28]

The SET involvement in the main-group metal hydride reducton of benzophenone derivatives was first reported by Ashby in 1980.[29] The reaction of AlH_3 with dimesityl ketone (DMK) produced a violet solution within a few minutes that exhibited a well-resolved EPR spectrum. The disappearance of the paramagnetic intermediate was found to have a rate constant within experimental error of the rate constant describing the appearance of the product. A probable mechanistic scheme involving a stable radical anion-radical cation pair as the intermediate was proposed as follows, see Scheme I-7.

$$AlH_3 + Ar_2CO \underset{\text{fast}}{\overset{k_1}{\rightleftharpoons}} [AlH_3^{\bullet+}][Ar_2CO^{\bullet-}] \xrightarrow[\text{slow}]{k_2}$$

$$Ar_2\dot{C}OAlH_2 \xrightarrow{H_2O} Ar_2CHOH$$

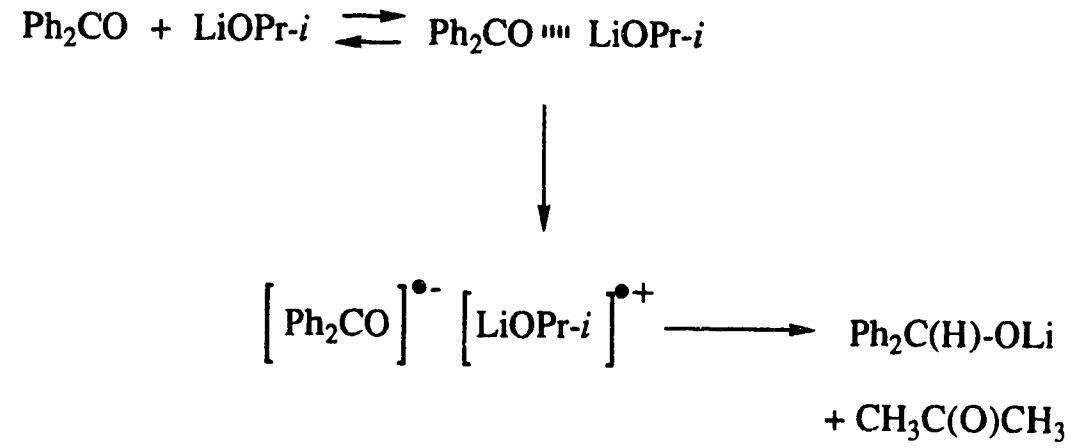
H

Scheme I-7

The same kinetic behavior of the EPR signal was observed for the reactions of DMK with metal hydrides MgH_2 and HMgX (X = Cl and Br).[29]

The evidence for SET in the reactions of either alkyl halides or ketones with R_3SnM (R = Me, Ph; M = K, Li, Na), R_2P^-, RS^-, OH^-, OR^-, RLi, enolates, $LiAlH_4$, and $LiCuR_2$ was also reported by Ashby.[30, 31] The possible involvement of a free-radical process in the reaction of

trimethylstannyl alkalis with alkyl halides was substantiated but also questioned by several other groups.[32,33] Reactions of various metal alkoxides LiOR (where R = *i*-Pr, *n*-Bu, *t*-Bu, and *t*-BuCH$_2$) with aromatic ketones produced intermediate ketyls. The observations were initially explained by the mechanism represented by the following equation (Scheme I-8).[34]



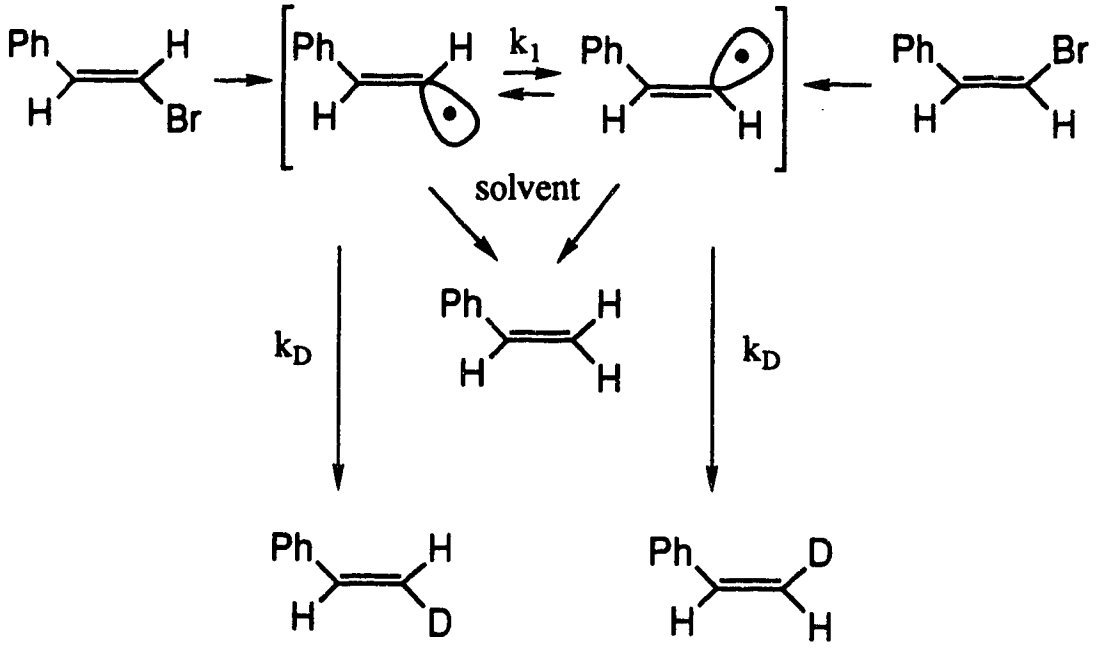
Scheme I-8

However, the SET reaction rate constant obtained from a calculation using the Marcus equation predicts that SET between Ph_2CO and *t*-BuO^- is not feasible. Any radicals must therefore arise by some other more complex mechanisms.[35]

Aluminum alkyls AlR_3 can undergo SET with suitable substrates as shown above. Species containing Al-H bonds such as AlH_3,[21,29] R_2AlH,[36] $LiAlH_4$,[17, 37] or $NaAlEt_2H_2$,[3] are generally much more reactive. Their electron transfer reactivities have been extensively investigated. The reactivity of $LiAlH_4$ has received particular attention in the past few

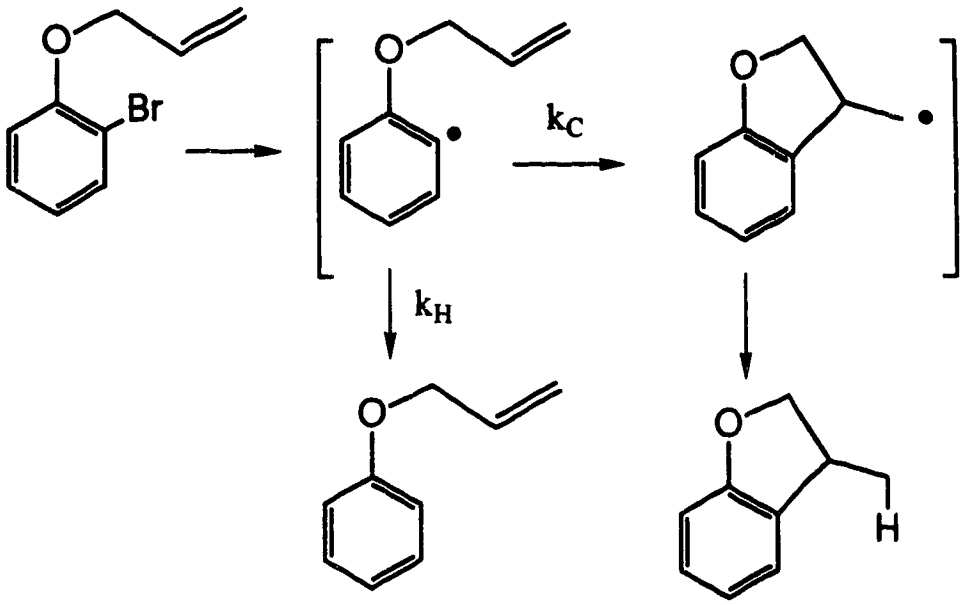
decades.[17,37,38,39,40,41] Evidence for a radical intermediate in the $LiAlH_4$ reaction was first reported by Chung and co-workers:[38]

i) The reduction of *trans*- and *cis*-bromostyrenes with $LiAlD_4$ (20 °C) proceeded with complete loss of stereochemistry regardless of the starting geometry or choice of solvent (diethyl ether or THF), while reductions carried out in refluxing THF proceeded with predominant retention of configuration. Secondly, a significant amount of nonlabeled styrene was produced, indicating that the intermediate was capable of abstracting hydrogen from both the metal hydride and the solvent. The results can be best rationalized by a mechanistic picture involving the two rapidly interconverting radicals as shown in Scheme I-9.



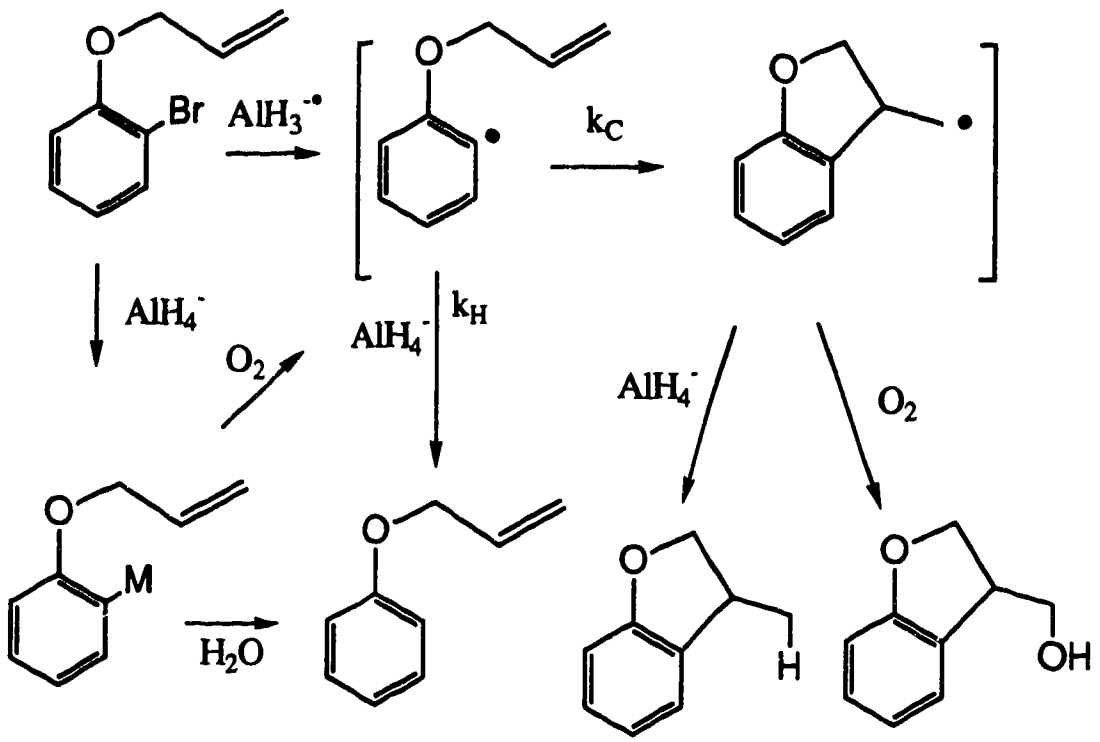
Scheme I-9

ii) Reduction of *o*-bromophenyl allyl ether with LAH yielded phenyl allyl ether and 3-methyl-2,3-dihydrobenzofuran, which suggested the involvement of radical intermediates in the reaction, see Scheme I-10.[39]



Scheme I-10

Further investigation conducted by Beckwith[40] indicated that the reduction of *o*-bromophenyl allyl ether with LAH proceeded by two competing pathways. One pathway which was promoted by oxygen involved aryl radicals, while the other pathway gave initially an arylmetal compound (Scheme I-11).[40]



Scheme I-11

The mechanism of the reaction of LAH with alkyl halides has recently been studied in detail by Ashby[31e,41d,f,42] using cyclizable radical probes. It is concluded that a SET-radical chain process is operative in addition to the halogen atom transfer process. However, Newcomb and Curran argued that the reduction of an alkyl iodide with LAH proceeds by a polar S_N2 mechanism.[43]

The photoinduced electron transfer reactivity of R_nMH_{4-n} (main group 4B, M = Si, Ge, Sn) with acceptors such as α-dicarbonyls or tetracyanoethylene (TCNE) was investigated.[44] Selective one-electron reductions of a cationic substrate, 10-methylacridinium ion, by group 4B bimetallic Me_3SnMMe_3(M = Sn, Ge, Si), have been investigated by

Fukuzumi and Kitano.[45] A radical chain reaction mechanism involving a SET process was proposed.

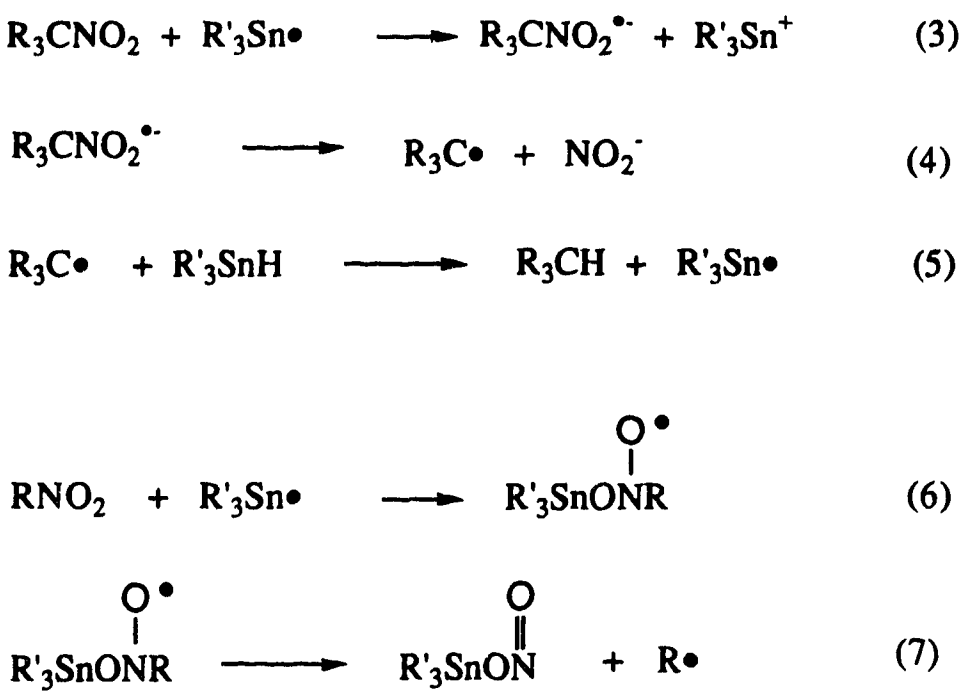
The trialkyltin hydride reduction of benzyl iodides was also shown to proceed via a chain reaction whose propagation sequence contained an electron transfer reaction, eqs 1-2 (Scheme I-12).[46]

$$ICH_2Ar + R'_3Sn\bullet \longrightarrow \bullet CH_2Ar + I^- + R'_3Sn^+ \quad (1)$$

$$ArCH_2\bullet + R'_3SnH \longrightarrow ArCH_3 + R'_3Sn\bullet \quad (2)$$

Scheme I-12

Tanner reported[47a] that the reaction between tri-*n*-butyltin hydride and a tertiary nitro compound proceeded by a chain reaction mechanism and resulted in the replacement of the nitro group by a hydrogen atom. The tin hydride reduction, as a variation of the Kornblum reaction, was initially thought to involve a SET between the stannyl radical and the nitroalkane, eqs 3-5[47a,b] (Scheme I-13). However, an alternative mechanism was also suggested[47e,f] in which the tin radical adds to the nitro compound to give a nitroxyl radical that, in turn, fragments to yield the chain-propagating alkyl radical, eqs 6 and 7.



$$R_3CNO_2 + R'_3Sn\bullet \longrightarrow R_3CNO_2^{\bullet-} + R'_3Sn^+ \quad (3)$$

$$R_3CNO_2^{\bullet-} \longrightarrow R_3C\bullet + NO_2^- \quad (4)$$

$$R_3C\bullet + R'_3SnH \longrightarrow R_3CH + R'_3Sn\bullet \quad (5)$$

or

$$RNO_2 + R'_3Sn\bullet \longrightarrow R'_3SnO(O\bullet)NR \quad (6)$$

$$R'_3SnO(O\bullet)NR \longrightarrow R'_3SnO(=O)N + R\bullet \quad (7)$$

Scheme I-13

More recently, Tanner[49] reported that the reductions of a series of α-halo ketones with triorganotin hydrides proceed by two distinguishable mechanistic pathways, both heterolytic hydride transfer and a homolytic electron transfer-hydrogen atom transfer chain sequence.

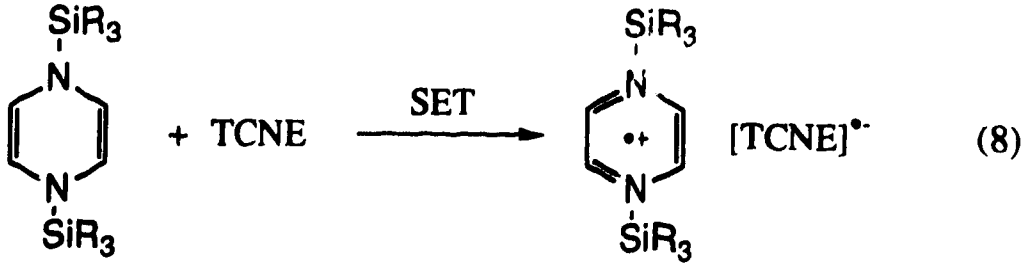
I-2. Experimental Methods Probing SET Mechanisms

Many mechanistic approaches have been developed in the past several decades to substantiate the involvement of SET reactions.[50] Among these approaches, EPR spectroscopy,[5] spin trapping,[51] chemically induced dynamic nuclear polarization (CIDNP),[6] deuterium[52] and carbon[53] kinetic isotope effects, chemical probes, and the use of Marcus theory[4,35,54] have

received much attention. The use of chemical probes has particularly been shown to be the most convenient method to establish the involvement of SET processes. A chemical probe[55] can be either a reagent or substrate which, upon SET, produces an intermediate (radical or radical ion) which subsequently gives radical-derived products. The products obtained are diagnostic of the intermediate. The chemical probes can be classified as stereochemical probes, radical rearrangement probes, and fragmentation probes, according to the nature of the secondary radical reaction. The advantage of using a chemical probe in mechanistic studies is the possibility of analysing the reaction kinetics quantitatively or semi-quantitatively from the known rate constants of the secondary radical reactions.

In this section, we discuss these approaches which are used to investigate the SET mechanisms, with emphasis on the use of EPR spectroscopy and chemical probes in identifying SET mechanisms.

1) **EPR Spectroscopy.** SET mechanisms of many SET reactions can be recognized by the fact that radicals, neutral or charged, can be detected directly or indirectly during the reaction or appear as products in a high yield. An example is given by Kaim[3,5d] who observed the formation of both a radical anion and a radical cation (EPR) in the reaction between tetracyanoethylene and 1,4-bis(trialkylsilyl)-1,4-dihydropyrazines (Scheme 1-14). The redox potentials (0.57 and -0.09 V) of the reactants predict the SET reaction.



(R= C_3H_7)

Scheme I-14

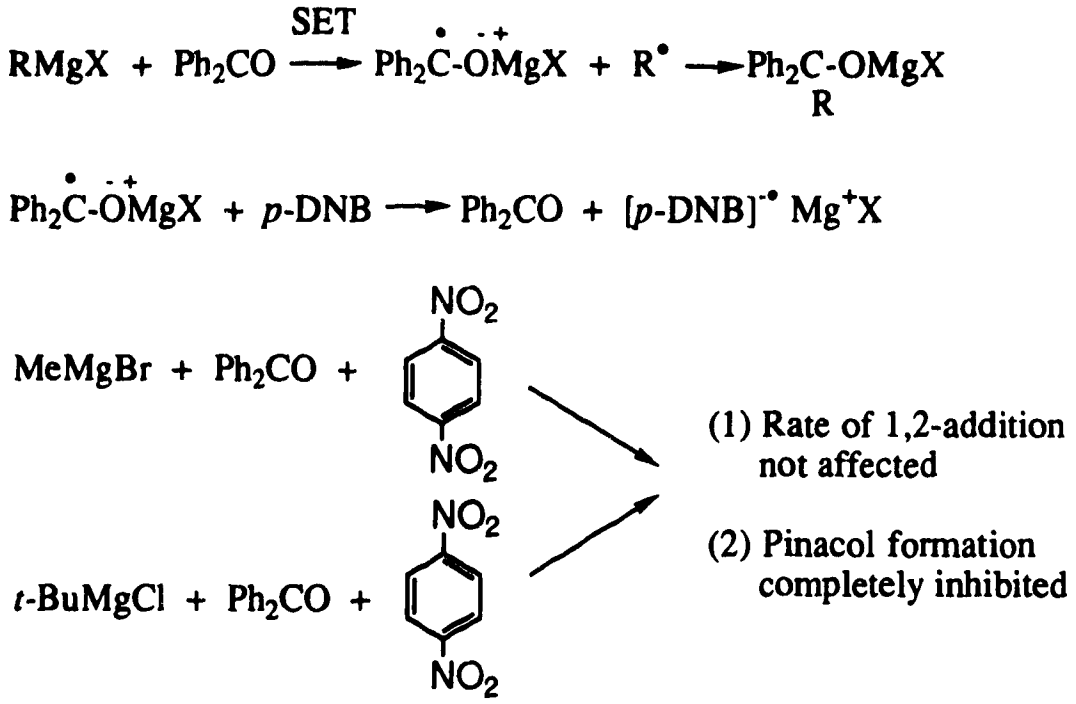
Since the pioneering work on the reaction between carbanions and closed-shell SET oxidants reported by Russell, Janzen and Storm[5a], EPR spectroscopy has been the most powerful technique available for the detection of paramagnetic species. Subsequent to that report the technique has been used extensively in the investigation of SET mechanisms.[5] As long as the odd-electron species observed by EPR are the major products of the reaction a SET reaction pathway is surely diagnostic of the major reaction pathway. However, it is more problematic, if one considers the appearance of low concentrations of transient radicals as evidence for a SET mechanism. If a radical intermediate can be identified it may have nothing to do with the main reaction path but only represent a minor side reaction, since the sensitivity of the method allows the detection of a very low concentration of radicals ($<10^{-7}$-10^{-8}M). Furthermore, EPR does not provide definitive information on how these paramagnetic species are formed. It is difficult to connect the appearance of a radical intermediate to a SET reaction.[5f,28,30a] It is therefore important that other methods, in particular product and kinetic analysis, are used to supplement the EPR

method, especially in the studies of reactions which can formally be rationalized as polar reactions.

2) Trapping of Intermediates by Radical Scavengers (Leading to the Inhibition of SET Processes). Spin trapping consists of adding a suitable radical scavenger (such as a nitrone or a nitroso compound) to the reacting system. The spin trap reacts with the radical of interest by addition to produce a more stable radical, detectable by EPR. The new spectrum will often depend upon the structure of the added radical and thus permits the identification of the unknown radical using EPR and NMR techniques. Spin trapping has been employed to detect transient radical[51,57] species formed during SET reactions.

Kornblum[56] reported that *p*-dinitrobenzene (*p*-DNB), which is more easily reduced than a conjugate ketone, will capture an electron from a ketyl radical anion whose conjugate ketone has a higher reduction potential. Ashby[15,58] also used *p*-DNB to capture an electron from a ketyl formed in the reaction between a Grignard reagent and a ketone. The results of the experiments showed that both MeMgBr and *t*-BuMgCl reacted with Ph_2CO at the same rate in the presence or absence of *p*-DNB, but that pinacol formation was completely inhibited by *p*-DNB. It was believed, therefore, that *p*-DNB would indeed capture the radical anion if it was free and that there was sufficient time for the reaction of the *p*-DNB with the ketyl to occur. However, the fact that the formation of the 1,2-addition product was not affected by *p*-DNB indicates that the ketyl was not free and a tight radical pair (ketyl anion-radical cation ($[RMgX]^{\bullet+}$)) was the intermediate

which leads to 1,2-addition product and hence could not be trapped by the *p*-DNB (Scheme I-15).



Scheme I-15

Radical intermediates such as alkyl or aryl radicals can also be trapped by electrophilic reagents such as olefins and oxygen.[59]

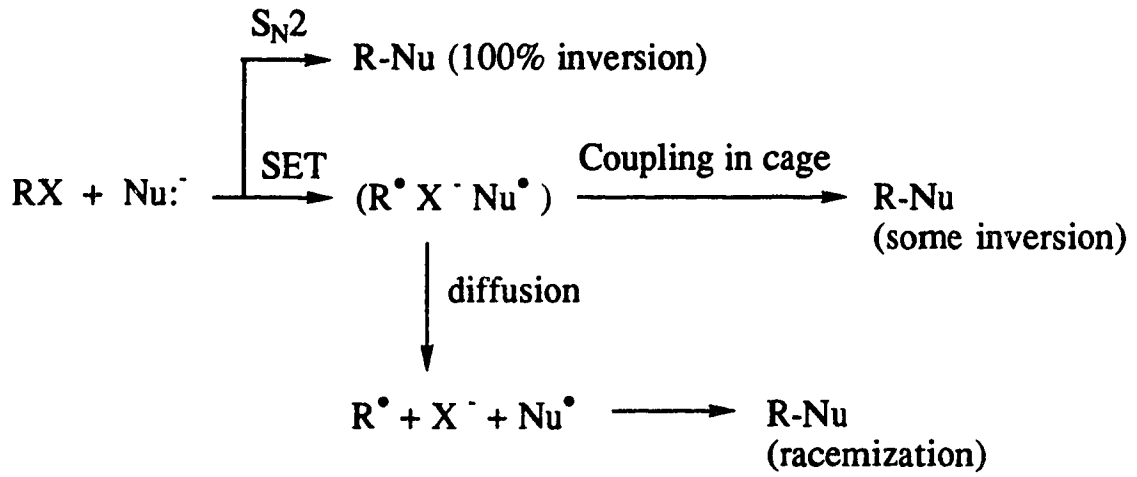
It should be noticed, however, that radical traps may be SET reactive in themselves and thus take part in unwanted SET reactions. For example, nitrosoaromatics and nitroxides are SET oxidants.[60]

3) **Stereochemical Probes.** Carbon-centered radicals usually possess a planar or pyramidal configuration with rapid inversion.[61] The inversion rate of free radicals decreases with the increasing s character of the

semioccupied orbital. The configurational stability of radicals has the order: vinyl radicals (sp^2-hybridized) > cyclopropyl radicals ($sp^{\sim 2.5}$-hybridized) > acyclic radicals (sp^3-hybridized).[62] When a reaction proceeds via neutral radicals one would expect that a chiral center should lose its optical activity within the solvent cage at a rate at least competitive with that of geminate coupling.[63] Therefore, the loss of stereochemical integrity can be an indication of radical intermediate formation. Thus, a method exists which can be used as evidence for intermediate formation of radicals in a reaction even when the radicals are not detectable by cyclization, trapping, or direct observation by EPR.[9] An example of the loss of the stereochemical integrity is illustrated by the reduction reactions of *trans*- and *cis*-bromostyrenes with LAD and LAH,[38] see Section 1.

Since the ease of reduction of RX compounds decreases in the order X = I > Br > Cl > OTs, reactions of alkyl tosylates are more likely to proceed by a S_N2 pathway whereas reactions of alkyl iodides are more likely to proceed by a SET. It was shown by using a chiral probe that the reactions of six nucleophiles (Nu:: LiSPh, LiCN, $LiPPh_2$, $NaSnMe_3$, and $LiAlD_4$) with optically active 2-substituted octanes (R*X, X = OTs, Cl, Br, and I) resulted in a loss of optical activity of the products as the leaving group proceeded from tosylate to iodide.[64] The reaction of optically active *sec*-alkyl iodides with lithium organocuprate reagents (Ph_2CuLi, Et_2CuLi, $Et_2CuCNLi_2$) gives racemic products whereas the reaction of the corresponding bromides gives products with complete inversion.[65] However, there is evidence that a reaction which exhibits substantial radical character can proceed with predominant inversion of configuration. The reaction of Me_3Sn^- with (+)-2-bromooctane resulted in 77% inversion of

configuration in the substitution product, and yet a similar reaction involving 6-bromo-1-heptene produced a 70% yield of cyclized substitution product.[31d] The competition between the normal S_N2 mechanism and a SET mechanism for the reaction between the optically active R*X and Nu: is as follows (see Scheme I-16):



Scheme I-16

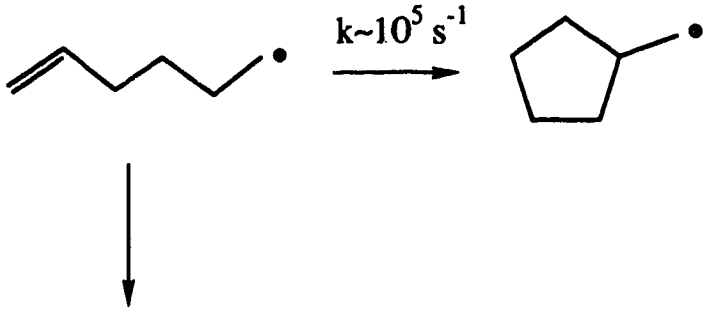
It is obvious that it is only the complete loss of stereochemical integrity that gives evidence for an unambiguous SET mechanism. The retention of stereochemistry in a reaction cannot be used as exclusive evidence which rules out the involvement of radical intermediates. Retention of stereochemistry has been observed in the reaction of α-chloro and fluorocyclopropyl radicals with radical scavengers such as tin hydrides, bromine, and bromotrichloromethane,[41a,66] even though cyclopropyl radicals have large inversion rates (10^6-10^{11} s^{-1}).[67]

4) Formation of Radical-Derived Products.

A classical approach for the elucidation of a mechanism is product analysis. The generation of dimeric products from a monomeric starting material is an indication of the involvement of radical intermediates. A well-known example is the dimerization of trityl radicals.[68] Other examples are shown by radical rearrangements such as the cyclization of the 5-hexenyl radical[31e,41d,f,42] which has been discussed in part in Section 1 of this Chapter and will be further discussed in the following section.

5) Kinetic Approach Based on the Radical Rearrangement Probes and the Fragmentation Probes etc.

The most critical part of a mechanistic study is the kinetics of the reaction. Radical clocks[69] based on skeletal rearrangements have been widely used as mechanistic tools in the investigation of radical reactions. The cyclizable radical probe has been used extensively in the elucidation of the SET involvement in which the formation of radicals is suspected. The 5-hexenyl radical, which cyclizes with a rate constant of ca. 10^5 sec^{-1},[70] is a sensitive probe for the intermediacy of radicals (Scheme I-17). Ingold described the use of this and similar cyclizations as "radical clocks" based on the determined rates of cyclization.[69]



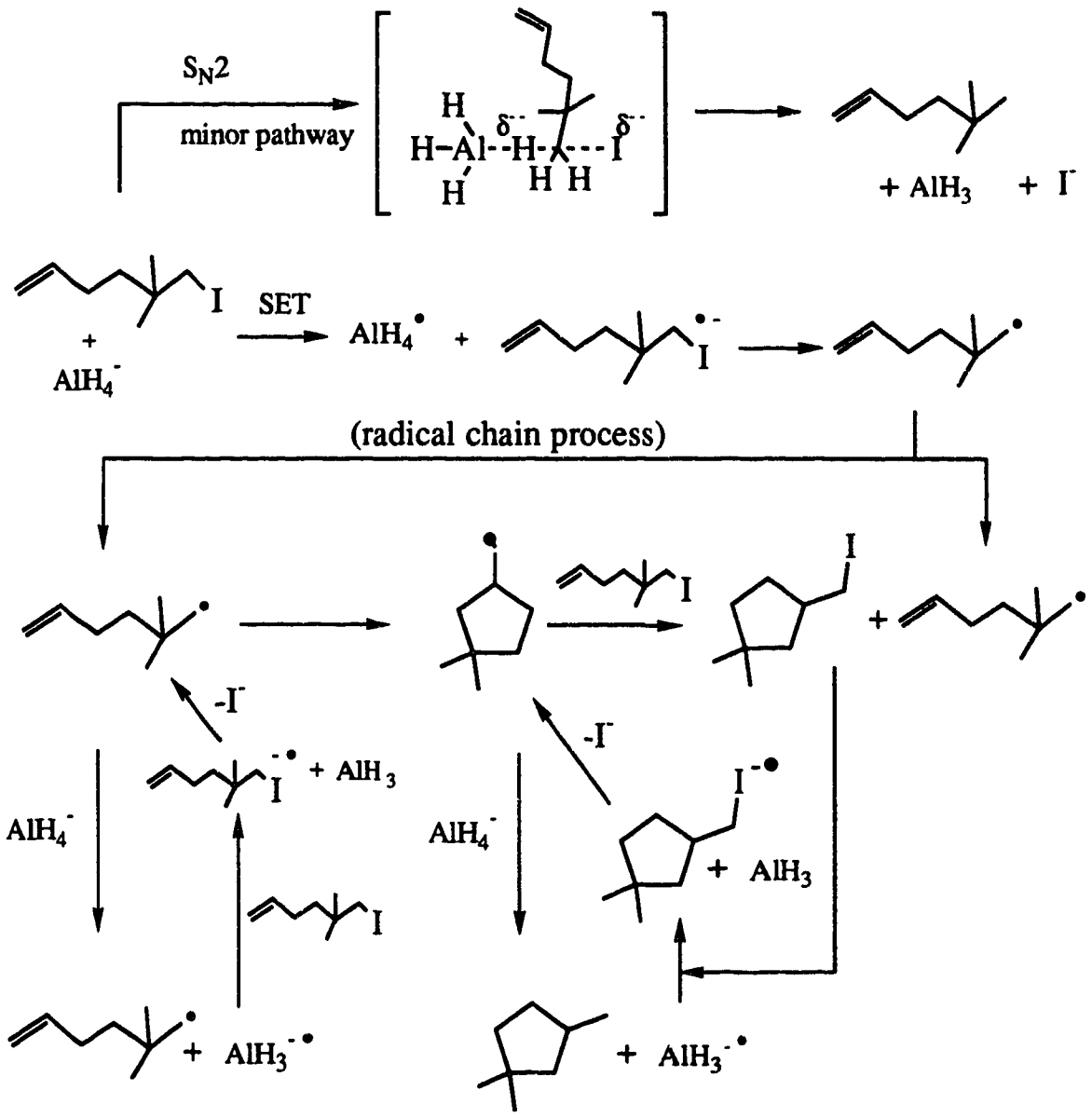
Non-cyclized product(s)

Scheme I-17

Ashby[31a] used 6-iodo-1-heptene, 2-iodo-*cis*-bicyclo[3.3.0]octene, and 5,5-dimethyl-6-iodo-1-hexene in the investigation of SET in the reaction of lithium dimethylcuprate with alkyl halides. Considerable amounts of cyclized products were found to be formed by a free radical chain process. Extensive trapping of the free radicals by hydrogen atom donors indicated that a substantial concentration of free radicals was produced in the reaction. These free radicals were believed to be produced by SET between the cuprate and the alkenyl iodides.

The SET reactions of a series of hydride reagents such as $LiAlH_4$, AlH_3, and $NaBEt_3H$ etc., were studied by using the cyclizable probe 6-iodo-1-hexene and its derivatives.[9,42] It was concluded that the LAH reduction of secondary alkyl iodides and hindered primary alkyl iodides occurs by a SET pathway. There was no evidence that SET was involved in reactions of alkyl chlorides or bromides with LAH in THF at 0-25 °C in the absence of a catalyst, although alkyl chlorides and bromides can react by SET with certain nucleophiles (*e.g.*, Me_3Sn^-). Unhindered primary alkyl iodides react with LAH by a SET pathway, and the S_N2 pathway was believed to be the

minor pathway. It was suggested that a radical process (hydrogen atom transfer) in addition to a halogen atom transfer process was involved in the reaction. A detailed mechanism of the SET reaction of 6-iodo-5,5-dimethyl-1-hexene with LAH was proposed by Ashby, see Scheme I-18.[42]

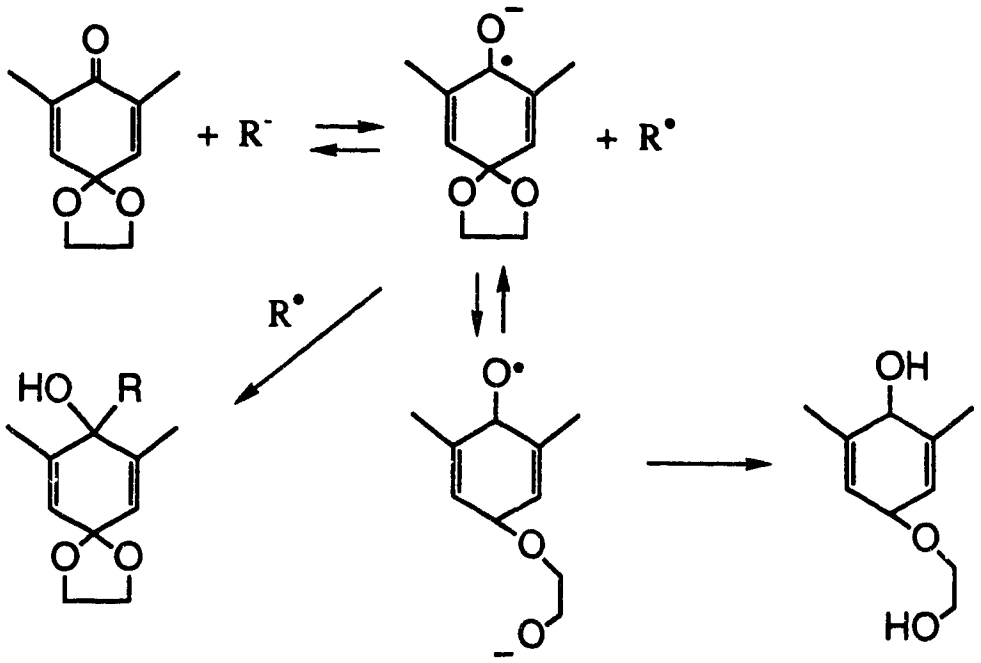


Scheme I-18

When cyclizable probes are used to determine the presence of a SET process in a reaction, the observation of cyclized products may not always indicate a radical process which is due to the reagent. The absence of cyclized products does not necessarily give evidence for the opposite conclusion. The lack of cyclization of the probe could be due to rapid geminate coupling of the radicals inside the solvent cage. One interesting example is the reaction of 6-bromo-1-hexene with $NaSnMe_3$, no cyclized product was observed, however, significant amounts of cyclized products were formed when the same reaction was carried out using THF-Et_2O (1:1) and THF-pentane (1:1).[31d]

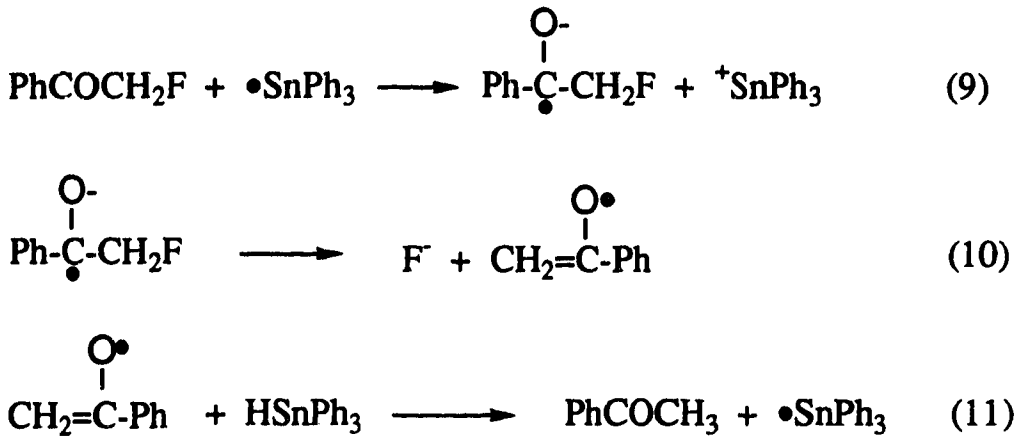
Some problems were observed recently in using alkenyl halides as cyclizable probes for SET processes, since the rearranged products can be formed via a sequence involving a fast radical chain isomerization of the alkenyl halide (especially iodides) probe initiated by very small amounts of radical sources.[43,71] Furthermore, the corresponding anions (as organometal derivatives of the alkyl halides) also cyclize, but at a much slower rate.[43,72]

A radical fragmentation probe, α-ethylenedioxy dienone, has been recently shown to be useful for the study of some reactions of organometallic reagents (see Scheme 1-19 below). The formation of ring-opened products by carbon-oxygen bond cleavage is indicative of a SET mechanism in the reactions of LiR, R_2CuLi , and RMgX. It was shown that 70% of ring-opened product and 25% of ring-unopened product were produced from the reaction between *t*-BuLi and the dienone probe in THF/TMEDA.[73]



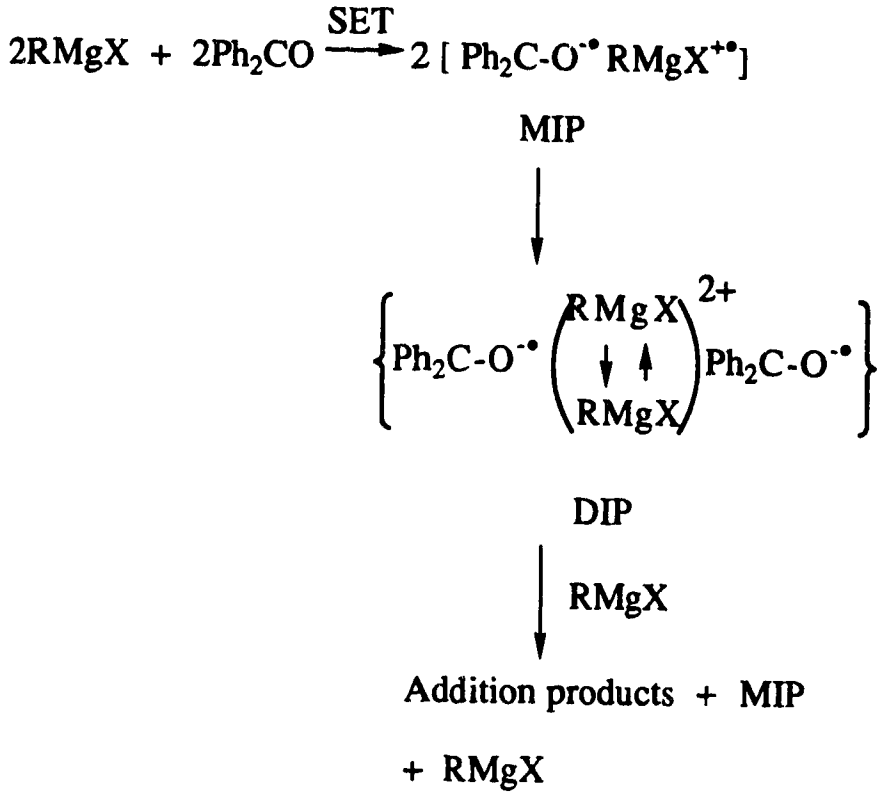
Scheme I-19

Fragmentation probes, α-haloacetophenones, have been extensively used by Tanner in the study of organotin hydride reduction reactions[49] and in the studies of NADH coenzyme model systems.[74] Reduction of α-haloacetophenones by organotin hydrides proceeds by homolytic and heterolytic pathways. The heterolytic reaction (a polar process) leads to α-(halomethyl)benzyl alcohol, while the homolytic pathway yields acetophenone via an electron-transfer-H atom abstraction mechanism. The mechanism for the conversion of α-fluoroacetophenone to acetophenone was suggested to be as follows, see Scheme I-20.[49]



Scheme I-20

Stopped-flow techniques, in conjunction with EPR spectroscopy, have been employed by Maruyama[75] for the direct study of the reaction between a Grignard reagent and benzil. It was suggested that the transient monomeric ion radical pair (MIP) formed between benzil and a Grignard reagent (RMgX) immediately dimerizes to a triplet radical dimer (DIP), in which two $RMgX^{\bullet+}$ formed a spin-paired, bridged dication (Scheme I-21). The participation of a second molecule of the Grignard reagent was found to be necessary for alkyl (or aryl) transfer from the dication to the radical anion. The same type of mechanism was proposed for the reaction of benzophenone with a Grignard reagent.[75]



Scheme I-21

Walling[76] presented a kinetic analysis using reasonable rate constants which were assumed for the reaction of the Grignard reagent with aromatic ketones. The analysis suggests that cage coupling is not necessary to account for the production of the 1,2-adduct. The diffusionally separated radicals (R·), if formed, presumably have enough time to undergo a rearrangement (*i.e.*, cyclization) if the rearrangement rate constant is larger than 10^5 s^{-1}. The rearranged radicals can couple with the ketyl to yield the addition products.

More recently, carbonyl carbon[14] kinetic isotope effects (KIEs) and substituent effects have been determined by Yamataka[53a,c] and co-workers

for the reaction of benzophenone-7-^{14}C with organolithium reagents (LiOPr-*i*, MeLi, LiPh, LiR, Me_2CuLi) and Grignard reagents (RMgX, R = Me, Ph, *o*-$CH_3C_6H_4$, CH_2Ph, *t*-Bu, $CH_3CH{=}CHCH_2$ and $CH_2{=}CHCH_2$), to distinguish the SET rate-determining reaction from the radical-coupling (RC) rate-determining one in the SET-RC sequence. It was suggested that for the reactions of benzophenone with LiR or with allylic Grignard reagents[53a,c] the absence of a ^{14}C KIE, a small ρ value, and the absence of steric rate retardation due to *ortho* substituents in the reaction is indicative of a rate-determining SET process.

In addition to these approaches, chemically induced dynamic nuclear polarization (CIDNP)[6] has been used to detect radical intermediates in SET reactions. The recent development of Marcus theory allows the calculation of SET reaction rate constants. The calculated rate constants have been compared with the experimentally observed rate constants in order to predict whether the SET reactions are feasible.[35,54]

6) Conclusions.

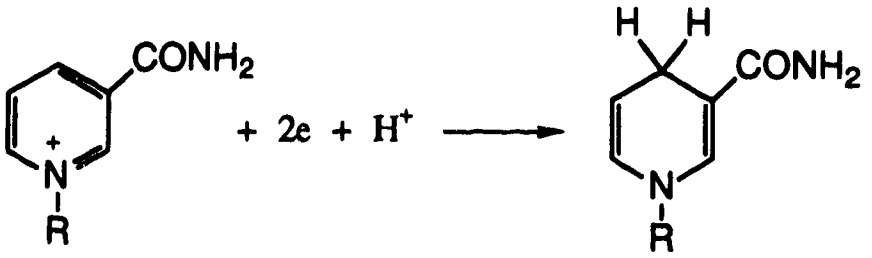
In summary, many approaches have been developed and applied to the investigation of SET reaction processes of main-group organometallics, but systematic studies of SET processes have been carried out with only a few main-group organometallics.[3,8,9,15,35] Although spectroscopic techniques such as EPR spectroscopy[69,77] and CIDNP[78] provide direct evidence for the involvement of radical intermediates in the reactions, chemical probes, which establish the relationship between radical intermediates and the products, should allow a differentiation between polar and SET pathways to be analyzed quantitatively or semi-quantitatively.

Since a high yield of radical-derived products indicates that the reaction proceeds mainly via a SET pathway,[79] the use of chemical probes in the elucidation of SET mechanisms has attracted much attention in recent years. Further understanding of the detailed mechanism of a specific reaction of main-group organometallics would be expected if new chemical probes are employed in conjunction with spectroscopic techniques in investigating these SET reactions.

I-3. Research Proposal

1) Some More Background of the Proposal.

The redox system NADH/NAD^+ is an important coenzyme in biochemical oxidation and reduction transformations. The mechanism of reduction by NADH or NADPH (or models of them, like N-benzyl-1,4-dihydronicotinamide, BNAH, and its analogues) has been of interest for the past few decades.[80] Investigations have been centered on the problem of distinguishing between a mechanism involving hydride transfer or single electron transfer-hydrogen atom abstraction. Several mechanistic pathways including SET processes have been suggested for the formal hydride transfer from BNAH to carbonyl compounds.[81]



(12)

R = adenine diphosphoribosyl

Miller[82] and co-workers, using Marcus theory, determined that NADH had an E°(NADH$^{+\bullet}$/NADH) = 1.02V. Marcus theory as applied to this problem indicates that a hydride transfer process is preferred when NADH or BNAH is allowed to react with substrates such as CF_3COPh, BNA^+, *p*-benzoquinone, $Cl_3CCOCCl_3$, N-Me-acridinium, 2,6-dichloro-*p*-benzoquinone, chloranil, and flavin models.[80,83]

More recently Tanner[74] demonstrated that a SET-hydrogen atom abstraction mechanism is operative in the reduction of NADH model, BNAH, by using fragmentation probe α-haloacetophenones. The mechanistic pathways are distinguished on the basis of the products formed since acetophenone is the product of a SET chain sequence and the halohydrin is the product of a hydride transfer sequence. Only acetophenone is formed in the reaction of α-haloacetophenones with BNAH and its analogues in acetonitrile at 61°C. The reduction can be initiated by a free radical initiator, AIBN, and inhibited by an inhibitor, *m*-DNB. The results are consistent with the SET chain mechanism. The co-enzyme NADH itself can reduce α-bromoacetophenone in aqueous solution to give acetophenone via a similar chain mechanism. The enzyme (HLADH)-mediated NADH reduction of α-haloketones produces the optically pure α-

halohydrins. The conclusion is that the enzymatic reductions proceed by a direct hydride transfer mechanism.[74b]

2) Scope of the Thesis.

Lithium tetrakis(N-dihydropyridyl)aluminate (LDPA),[84] formed from a reaction of LAH and pyridine, reduces aldehydes and diarylketones[84] and produces 3-substituted pyridines[85a-b] readily from alkylhalides or halogens. Since LDPA has both 1,2- and 1,4-dihydropyridyl ligands, it may serve as a proper inorganically bound model for NADH.[85c-f] The structure of LDPA was reexamined and an investigation of the mechanism of formation was carried out,[86] see Chapter 2.

Some questions are raised: i) Does LDPA serve as an inorganically bound model for NADH? ii) Is SET involved in its reactions?[87] and iii) If so, is SET the sole reaction path or a minor side reaction process. The reactivity of LDPA was examined by EPR spectroscopy and by its observed reactions with a series of chemical probes. Mesityl phenyl ketone (MPK), dimesityl ketone (DMK), bromotriphenylmethane, and 2,6-di-*t*-butylbenzoquinone were used in the EPR investigations to test the possibility of SET from LDPA to organic substrates. 4'-Bromoacetophenone, 4-bromobenzophenone, 2-bromo-2',4',6'-trimethylbenzophenone, 4-bromo-2',4',6'-trimethylbenzophenone, 3-bromo-2',4',6'-trimethylbenzophenone, 3,3'-dibromo-2,2',4,4',6,6'-hexamethylbenzophenone, and 6-halo(Br, I)-1-hexenes were used, in the presence or absence of a free radical chain initiator (AIBN) and an inhibitor (*m*-DNB), to establish whether a SET-free radical chain mechanism is operative in the reduction reactions. Trapping experiments with 1-hexene and deuterium labelling experiments with

LDPA-d_{24} and/or THF-d_8 were carried out. The results are consistent with the involvement of free radical intermediates in the reactions of LDPA. Trapping experiments with DCPH were also carried out to establish the detailed SET mechanism for the reduction of aromatic ketones. All the results are discussed in Chapter 3.

Although there is a large amount of work, on dihydropyridine (DHP) chemistry[88], neither the unsubstituted 1,2-DHP nor the unsubstituted 2,5-DHP has been reported. 1,4-DHP is the only unsubstituted DHP that has been well characterized.[89] After 1,2-DHP, 2,5-DHP, and 1,4-DHP were successfully characterized, from the hydrolysate of LDPA, they were applied in the synthesis of several natural products. Two alkaloids, (±)-anatabine and (±)-anabasine, were generated from autoxidation of the hydrolysis products of LDPA. Deuterium labelling showed that the mechanism for the formation of (±)-anatabine is consistent with the biosynthetic pathway which was hypothesized by Leete.[90] These results are reported in Chapter 4.

As strong EPR signals are observed during the sodium borohydride reduction of bromotriphenylmethane or 2,6-di-*t*-butylbenzoquinone, it is of interest to investigate the reaction of borohydrides using the ketone fragmentation probes. A series of fragmentation probes, 4'-bromobenzophenone, 4-bromo-2',4',6'-trimethylbenzophenone, and 3,3'-dibromo-2,2',4,4',6,6'-hexamethylbenzophenone, was used to differentiate between polar and SET processes in the reduction of aromatic ketones with borohydrides ($NaBH_4$, $NaBEt_3H$). A free radical chain initiator and an inhibitor were used to examine a possible free radical chain mechanism. The results of this study are described in Chapter 5.

The hindered aromatic ketone probes, 4-bromo-2',4',6'-trimethylbenzophenone, 2-bromo-2',4',6'-trimethylbenzophenone, 3-bromo-2',4',6'-trimethyl benzophenone, 2,4,6-trimethylbenzophenone, 4-chloro-2',4',6'-trimethylbenzophenone, were also used for a study of the SET reaction processes of Grignard reagents (RMgCl, R = *t*-Bu, *n*-Bu, Me, Phenyl, 5-Hexenyl, and Allyl). Product analysis was performed to establish the SET mechanism and EPR experiments were carried out to substantiate the SET. The preliminary results of this study are reported in Chapter 6.

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But we found in our preliminary experiments[86] that Ashby's results were from a reagent ("LDPA") which was contaminated with $LiAlH_4$.

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CHAPTER 2

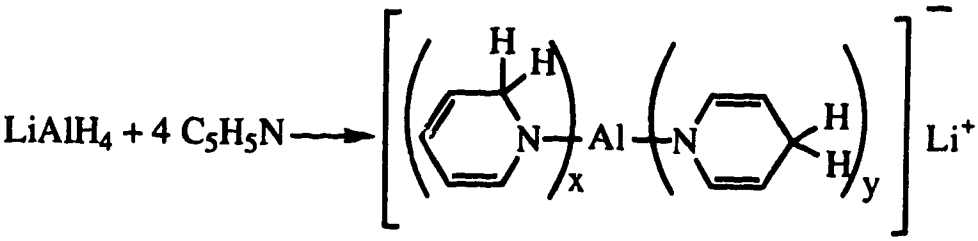
On the Structure and Mechanism of Formation of an Inorganic NADH Model, Lithium Tetrakis(N-dihydropyridyl)aluminate (LDPA)*,[1]

*. A version of this chapter has been submitted for publication.

Tanner, D.D.; Yang, C.-M. *J. Org. Chem.* **1992**, *57*, 0000.

Introduction

The reduction reactions of $LiAlH_4$ (LAH) in pyridine (Py) solvent were shown by Lansbury and Peterson to proceed selectively when the LAH and Py were mixed, "aged" prior to the addition of the hydride to a carbonyl-containing substrate.[2,3] The aged mixtures readily reduced certain aldehydes and ketones, but not carboxylic acids and esters. The reagent, which preferentially reduced highly electrophilic carbonyl groups, was subsequently shown to be lithium tetrakis(N-dihydropyridyl)aluminate (LDPA), **I**.[4] The structure of the newly formed reagent, **I**, was analyzed by ^1H NMR spectroscopy and found to have both 1,2- and 1,4-dihydropyridyl ligands (3.5 Py/LAH).



(1)

I

$x + y = 4$

The 1,4-dihydropyridyl was proposed to be the thermodynamically more stable ligand since when the reactants were mixed at 0°C and aged at different temperatures the complex showed a temperature dependent ratio of 1,4-/1,2-dihydro isomers which favored 1,4-bonding at higher temperatures, see Table II-1.

Table II-1. The Effect of Temperature on the 1,4-/1,2-Dihydropyridyl Ratio in I.[a]

Temperature, °C	-30	0	25	60
Ratio 1,4-/1,2	0.37	0.45	1.04	9.00

[a] Taken from ref. 4.

Since the reduction reactions of derivatives of dihydropyridine (DHP) have been of considerable interest both as model compounds for NADH reductions and for their use as selective reducing agents,[5] a study of the structure and reactivity of LDPA, an inorganically bound derivative of dihydropyridine, was undertaken.

Results and Discussion

The Reversible Formation of LDPA - The temperature dependent isomer distribution of the isomers of LDPA was reinvestigated and shown to be in qualitative agreement with the values reported by Lansbury.[4] When the reactants were mixed an exothermic reaction took place. In order to determine the thermodynamic distribution of the ligands in the LDPA complex the reactants were mixed and aged at each of the desired temperatures. When a complex formed and aged at a lower temperature was heated to a higher temperature in pyridine solvent the distribution of ligands (1,4-/1,2-) changed to that found in the complex formed at the higher temperature. Furthermore, the ratio of 1,4-/1,2-dihydropyridyl ligands was dependent on the temperature and time of "aging", see Table II-2.

Table II-2. The Effect of Temperature on the 1,4-/1,2-Dihydropyridyl Ratio in I.[a]

Temperature, °C	-30	0	23	61	61(23)[b]	90	90(23)[c]	90(0)[d]
Ratio 1,4-/1,2	0.19	0.47	0.62	0.73	2.45	2.53	7.40	>99

[a] The samples were prepared and aged for 5 days.

[b] A crystalline sample of LDPA prepared at 23 °C, (1,4-/1,2-) = 0.62, was heated in pyridine at 61 °C for 48 h.

[c] The 23 °C complex was heated at 90 °C for 48 h.

[d] The sample prepared at 0 °C (1,4-/1,2- = 0.47) was heated in pyridine at 90 °C for 100 h.

The reversible formation of LDPA established that the 1,4-dihydropyridyl complex is the product of thermodynamic control while the complex containing 1,2-dihydropyridyl ligands is the product of kinetic control.

The distribution of ligands in the LDPA complex was determined by integration of the 400 MHz ^{1}H NMR spectrum of the complex, Fig. II-1. The isomer distribution obtained from this analysis was presumably an average distribution of five isomeric aluminates, **II-VI**, Fig. II-2.

A typical ^{13}C NMR spectrum of LDPA is shown in Fig. II-3. An analysis of the 100.6 MHz ^{13}C NMR of a THF solution of the LDPA complexes formed at different temperatures allowed the assignment of the ^{13}C chemical shifts of the carbon-5 of the 1,2-dihydropyridyl ligands of 4 of the 5 isomeric LDPA complexes (**II-VI**) , see Fig. II-4. Since the 1,4-/1,2-ratio of ligands in LDPA formed at high temperature (90 °C) was >3 then all 1,4-dihydropyridyl complex must also have been present. Furthermore, the decoupled ^{1}H NMR spectrum of LDPA formed with either high or low 1,4-/1,2-ratios of dihydropyridyl ligands showed the same distribution of all five isomers, **II-VI**, as was determined using the ^{13}C NMR spectra. The protons at both the 2- and 6-positions of the 1,2-dihydropyridyl ligand, decoupled from their adjacent protons showed four separate peaks which corresponded to isomers **III-VI** (Fig. II-5). When the protons at C-2 of the 1,4-dihydropyridyl ligand were decoupled from their adjacent protons the four separate LDPA isomers **II-V** could be observed, see Fig. II-5.

When $LiAlD_4$ (LAD) was allowed to react with pyridine (23 °C) deuterated LDPA (LDPA-d4) was formed. The 30.7 MHz ^{2}H NMR

spectrum also showed that the product mixture contained small amounts of the 3 monodeuterated pyridines. When a crystalline sample of the tetradeuterated LDPA which contained occluded pyridine solvent was dissolved in fresh pyridine and heated for 7 days at 90 °C not only did the 1,4-/1,2- ratio of deuterated pyridyl ligands in the LDPA change, but the deuterium was also exchanged from the deuterated LDPA into the solvent pool, see Table II-3 and Fig. II-6a and Fig. II-6b.

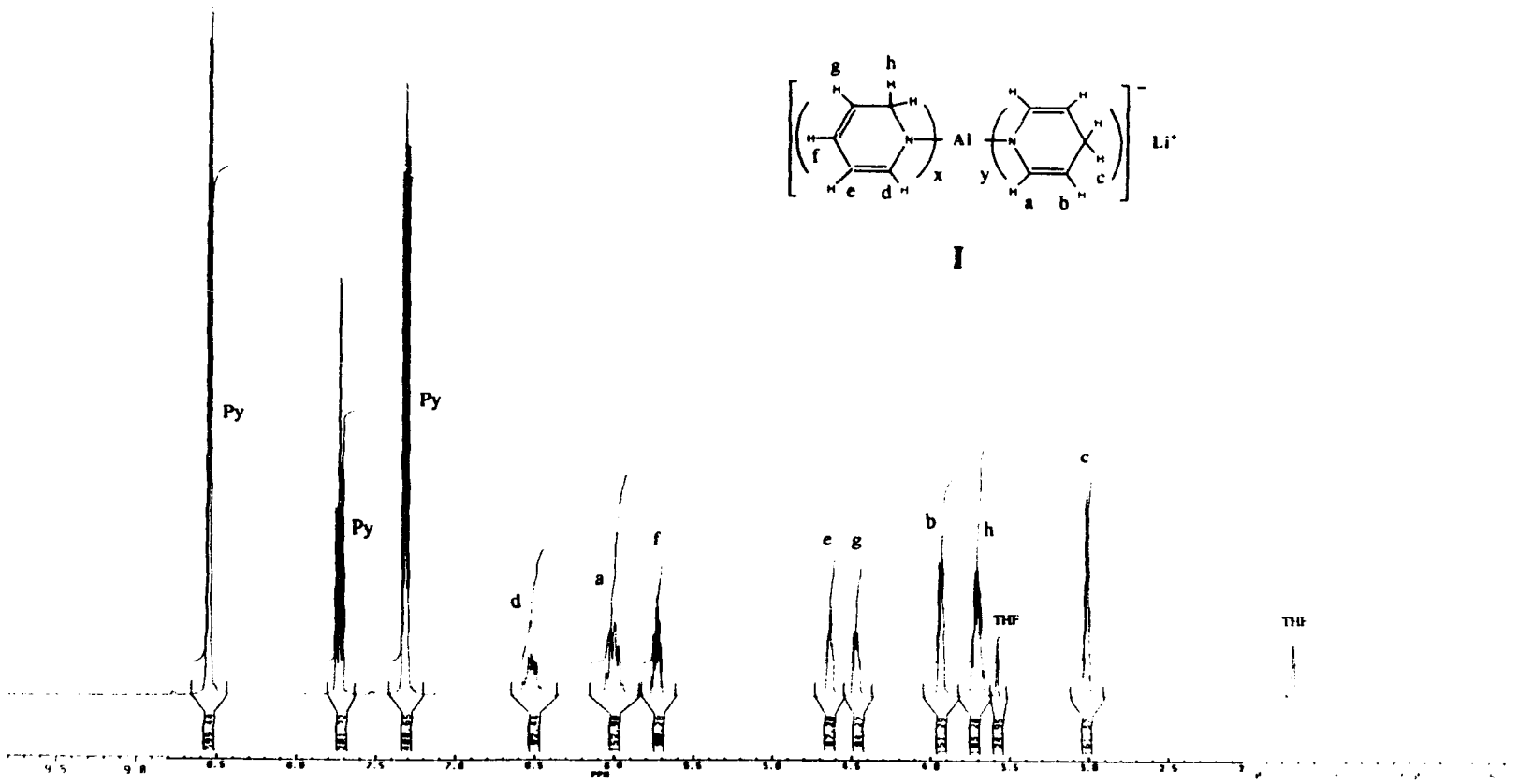


Fig. II-1. A Typical 400 MHz ^{1}H NMR Spectrum of LDPA (THF-d8).

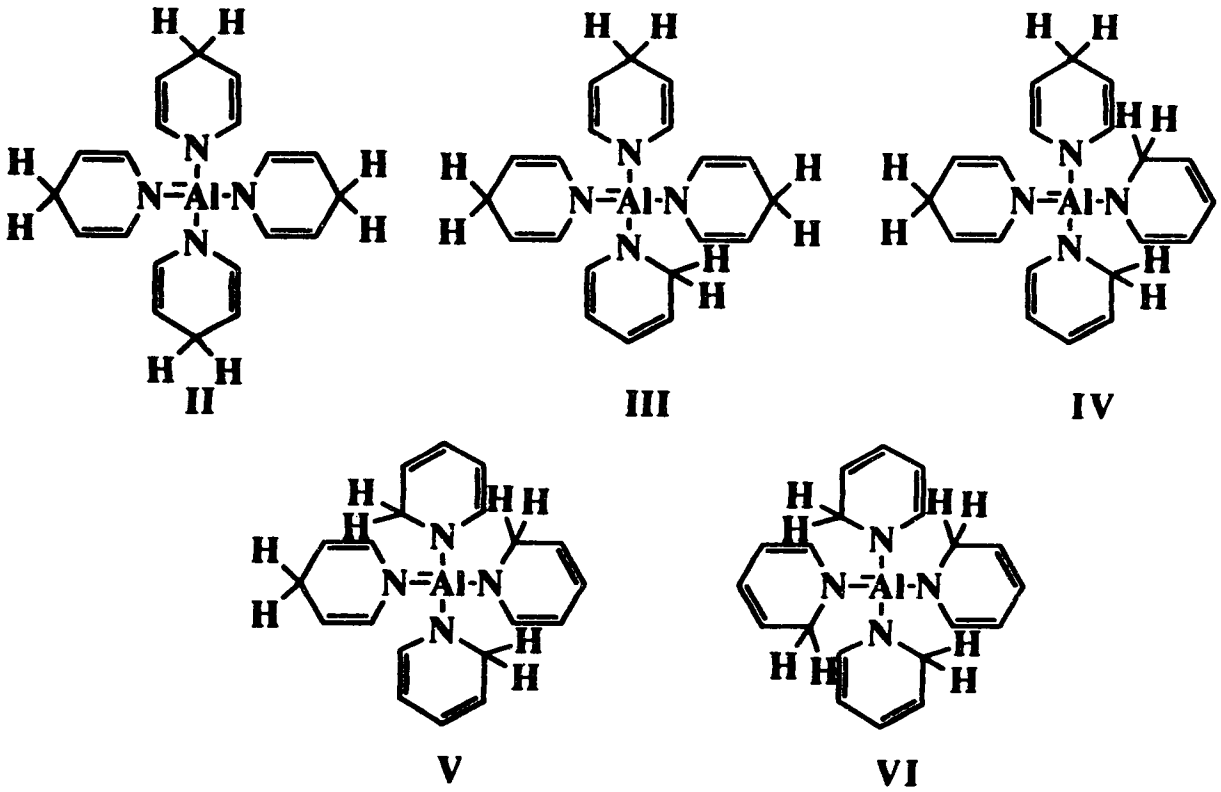


Fig. II-2. The Five (5) Isomeric Structures of the LDPA Anion.

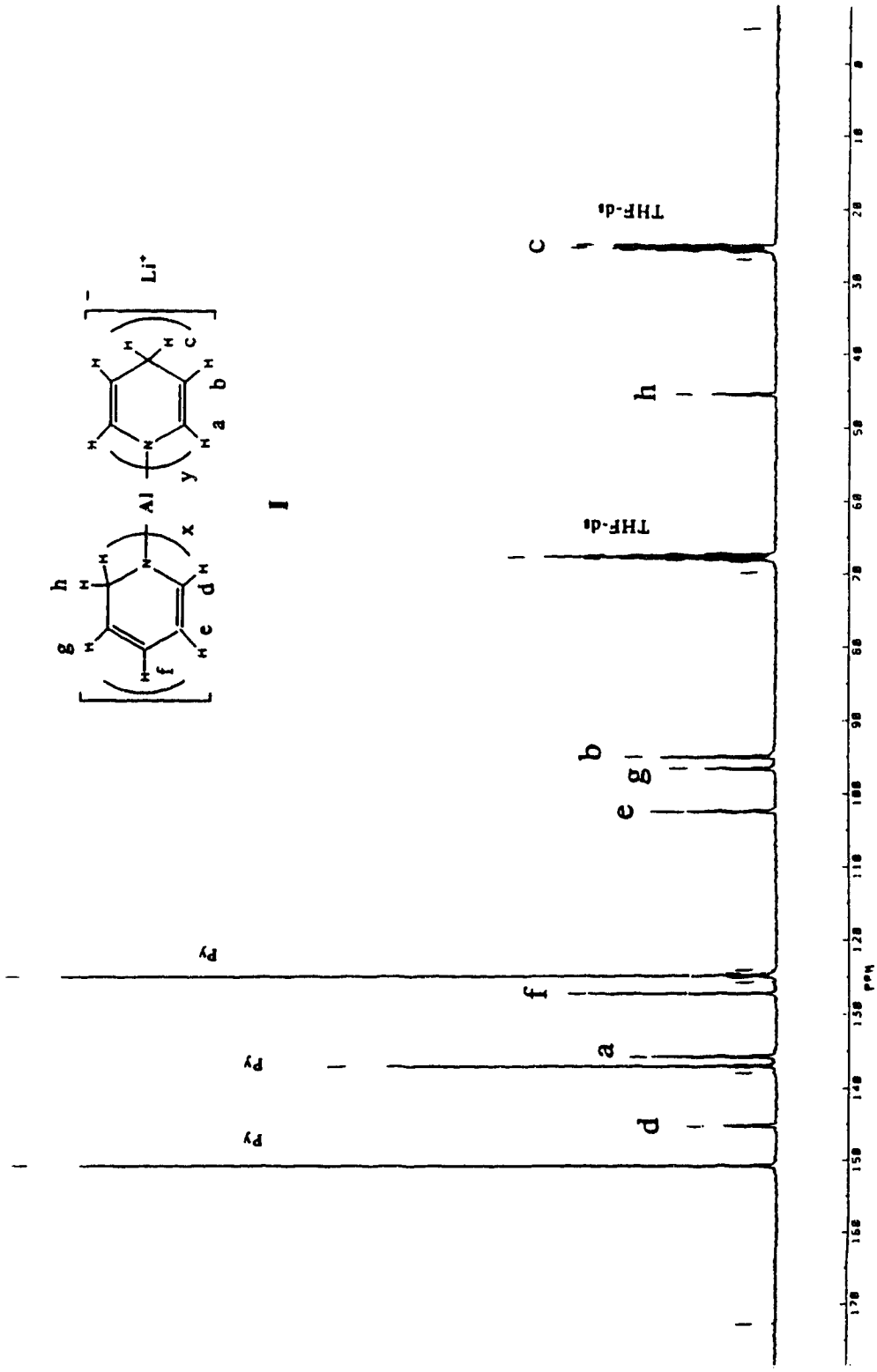


Fig. II-3. A Typical ^{13}C NMR Spectrum of the LDPA in THF-d8.

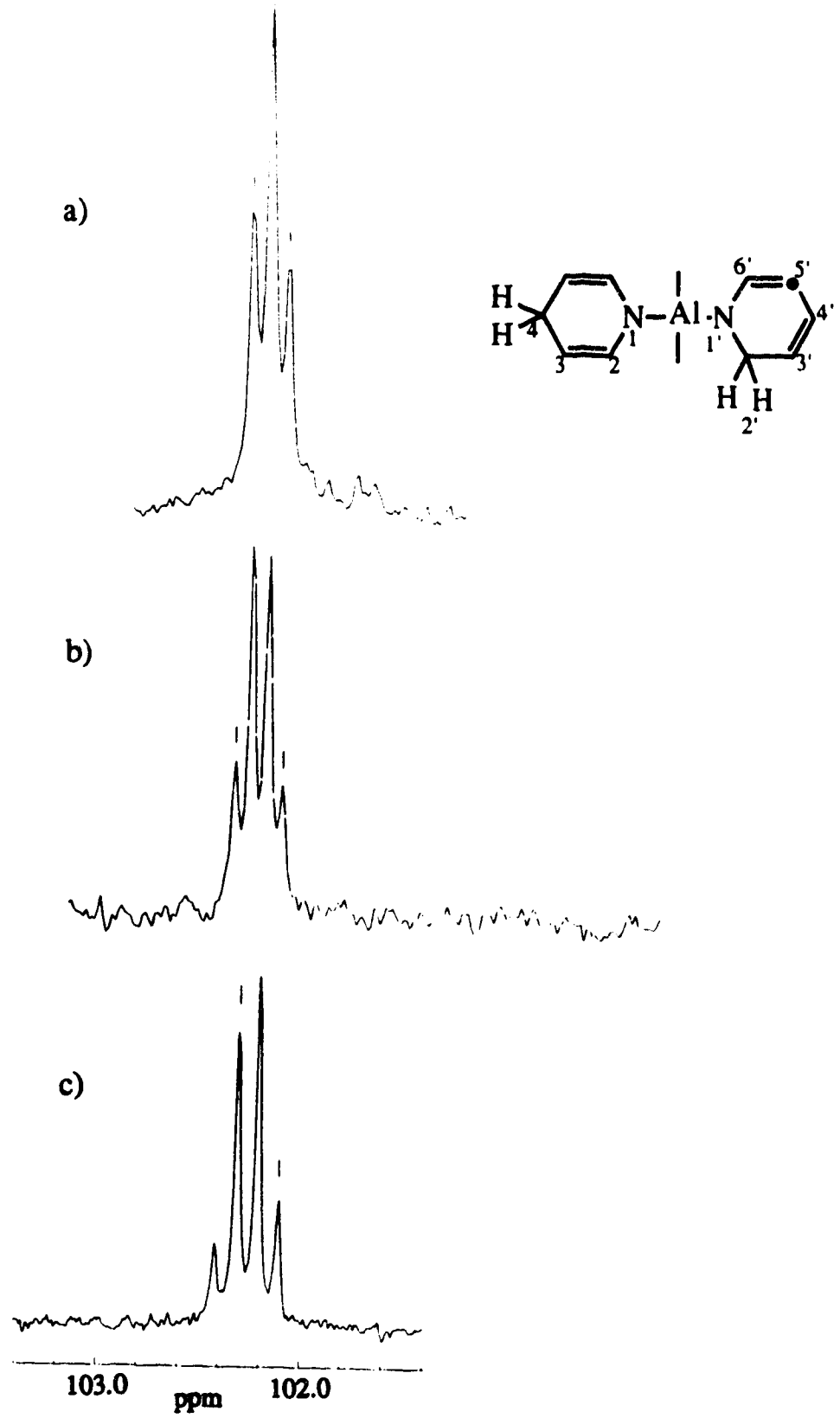


Fig. II-4. ^{13}C NMR Spectra (C-5', in the region of 102-103 ppm, THF-d_8) of LDPA Prepared at: a) 90 °C; b) 61 °C; c) 23 °C.

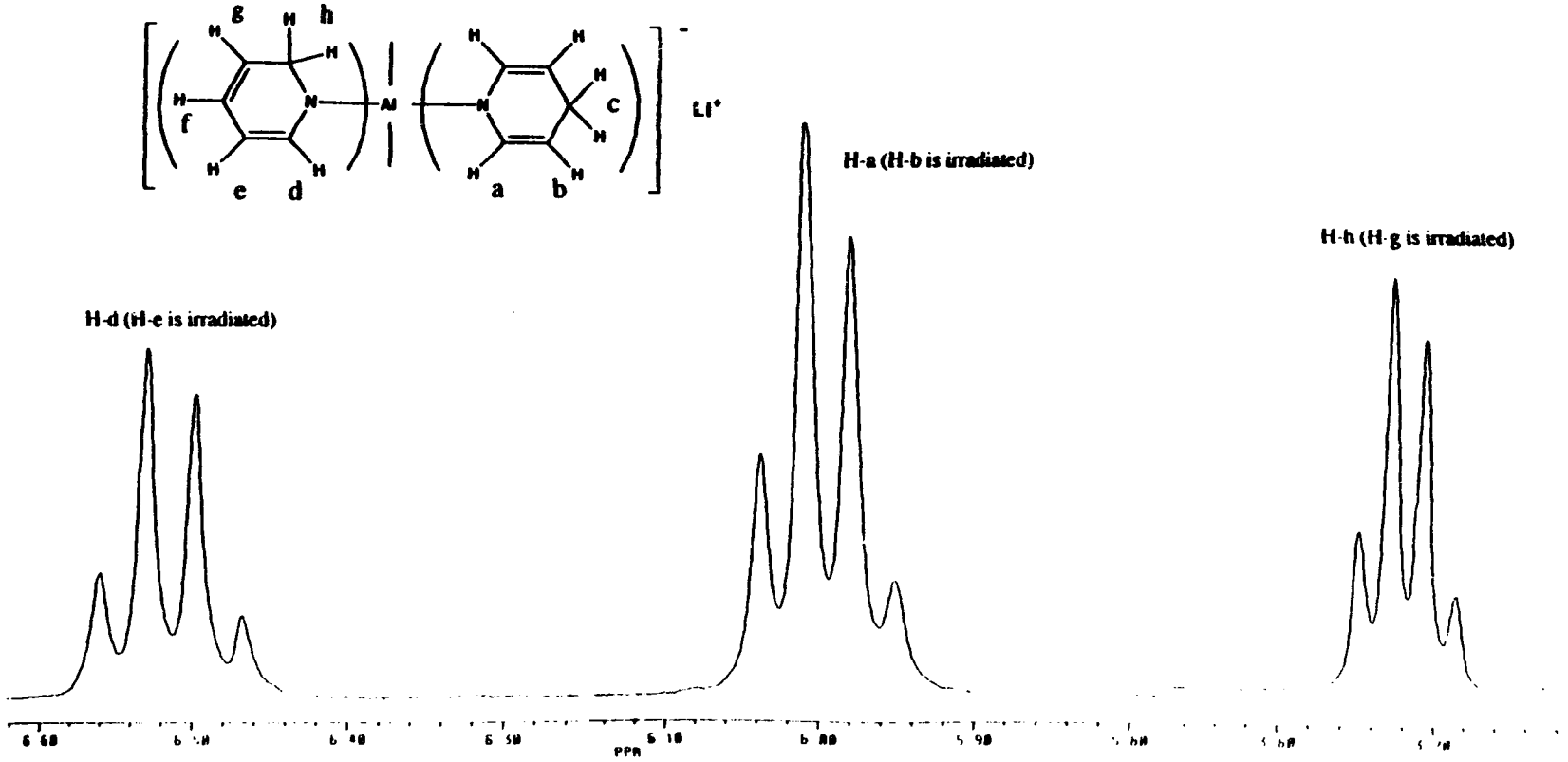


Fig. II-5. Parts of the Decoupled ^1H NMR Spectrum of LDPA Prepared at 0 °C(THF-d8).

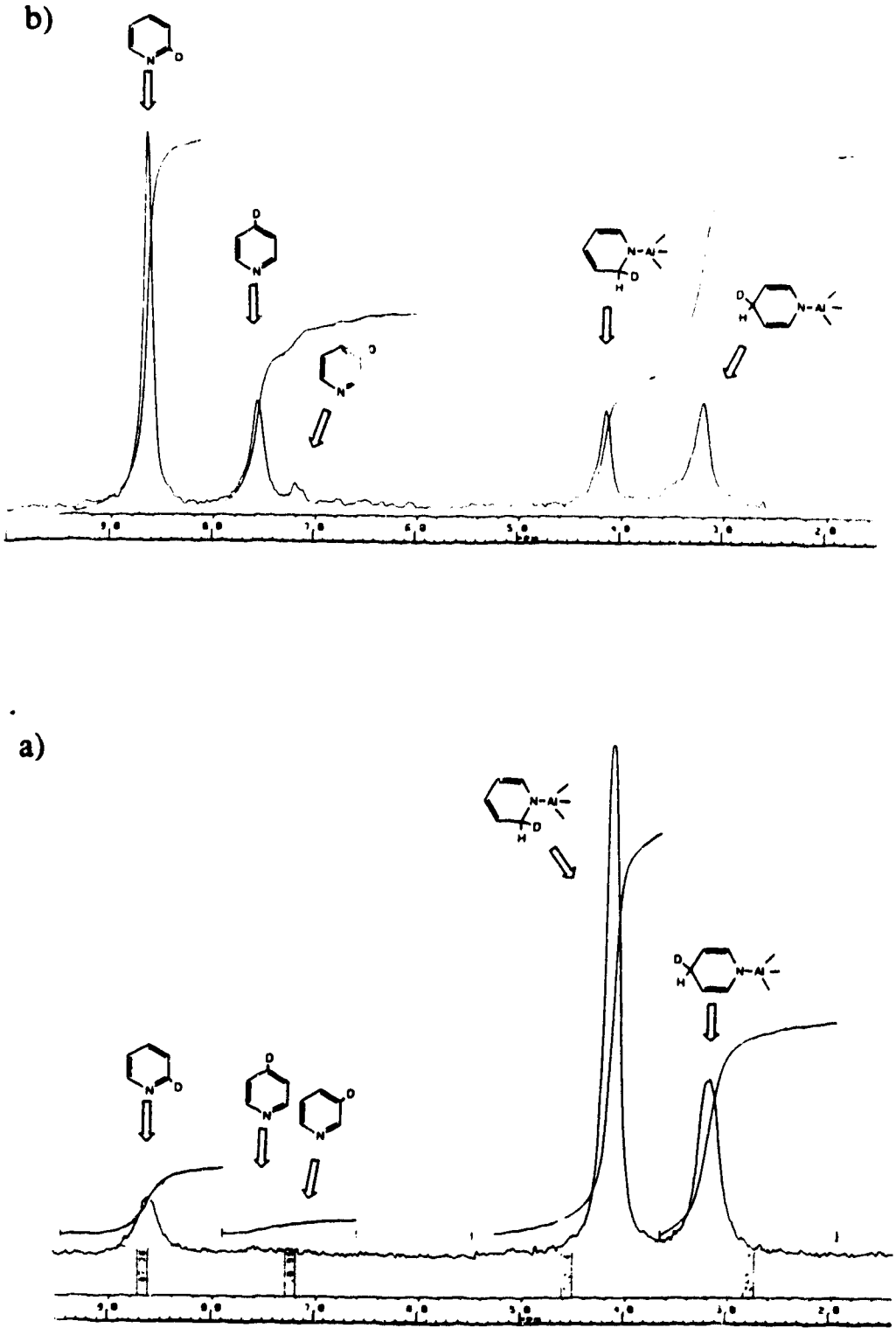


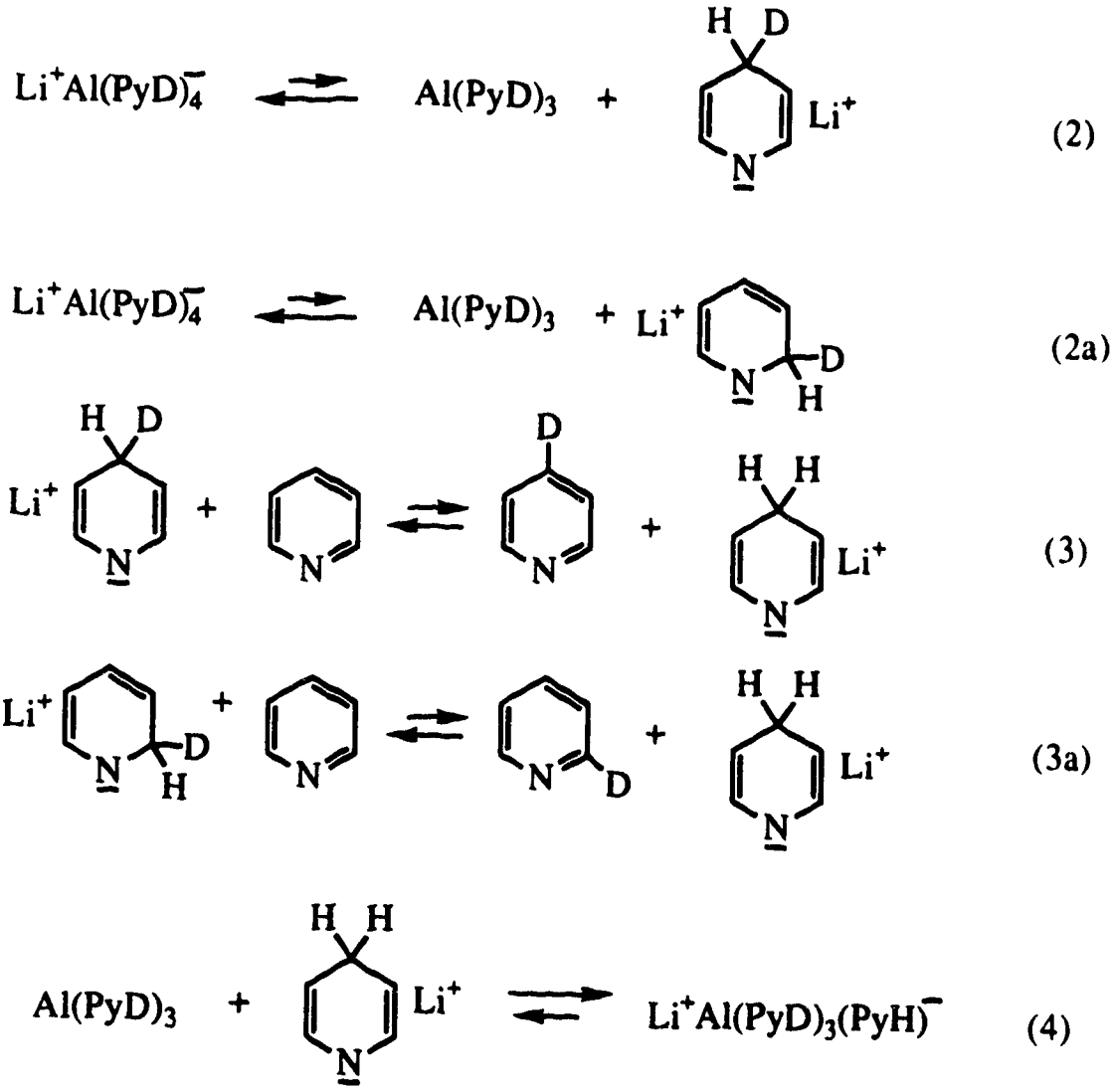
Fig. II-6. The ^2H Distribution in the Tetradeuterated LDPA (LDPA-d_4) - Pyridine Solution a) Before (25 °C) and b) After Heating (90 °C, 7 days).

Table II-3. The Deuterium Distribution in the Tetradeuterated LDPA Complex and the Solvent Pyridine Before and After Exchange.[a]

$LiAl(PyD)_4$		C_5H_4DN			
1,2-%	1,4-(%)	2-D-(%)	3-D-(%)	4-D-(%)	
58.3	30.8	9.7	0.4	0.8	(Before heating at 90 °C)
22.7	27.7	34.5	2.7	12.4	(4 days heating at 90 °C)
14.1	23.7	43.0	2.1	17.0	(7 days heating at 90 °C)

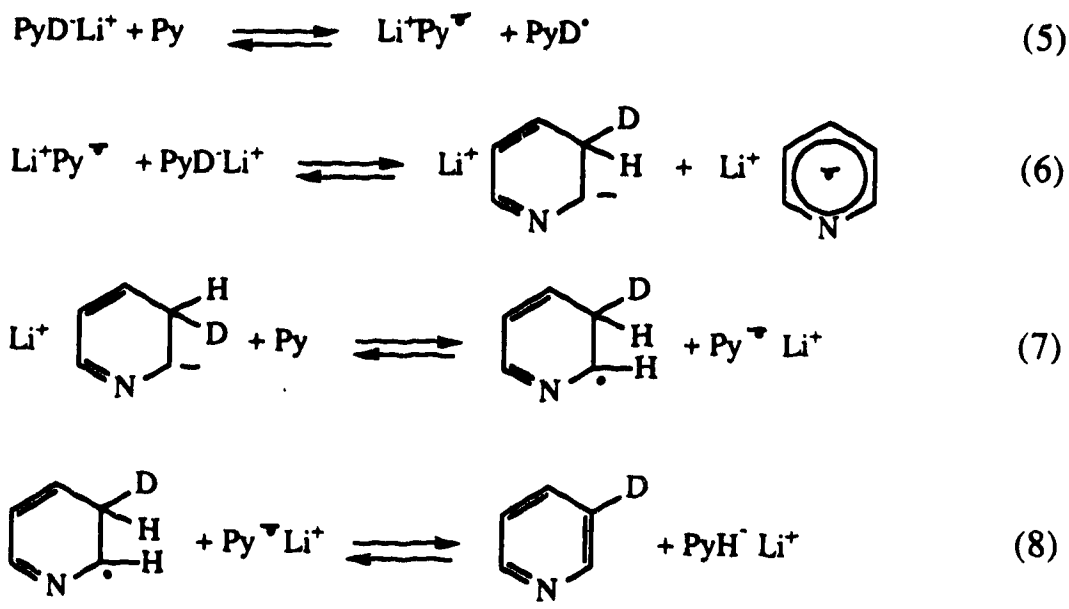
[a] Percentages were calculated from the integrated ^2H NMR spectra.

The deuterated pyridine was a mixture of three isomers with deuterium substituted at the 2-, the 3- and the 4-positions. A mechanism which proceeds via a polar hydride transfer process is expected to yield only 2- and 4- deuterated pyridine (Scheme II-1, eqs 2-4).



Scheme II-1

However, small amounts of 3-deuterated pyridine are also formed during the reversible exchange. A homolytic exchange mechanism which may account for these reversible processes is given in Scheme II-2 (eqs 5-8).



Scheme II-2

Although no EPR signals could be detected during the exchange reaction between LDPA and pyridine the involvement of a radical pathway was considered since it was consistent with substitution at the 2-,3- and 4-positions of the pyridyl radical anion. The intermediacy of a radical anion was confirmed when LAH was allowed to react with pyridine. An exothermic reaction took place when a degassed sample of pyridine and a THF solution of LAH were mixed in an EPR tube and the tube was placed in the cavity of the EPR spectrometer. A strong signal of the radical anion of pyridine was obtained (see Fig. II-7).

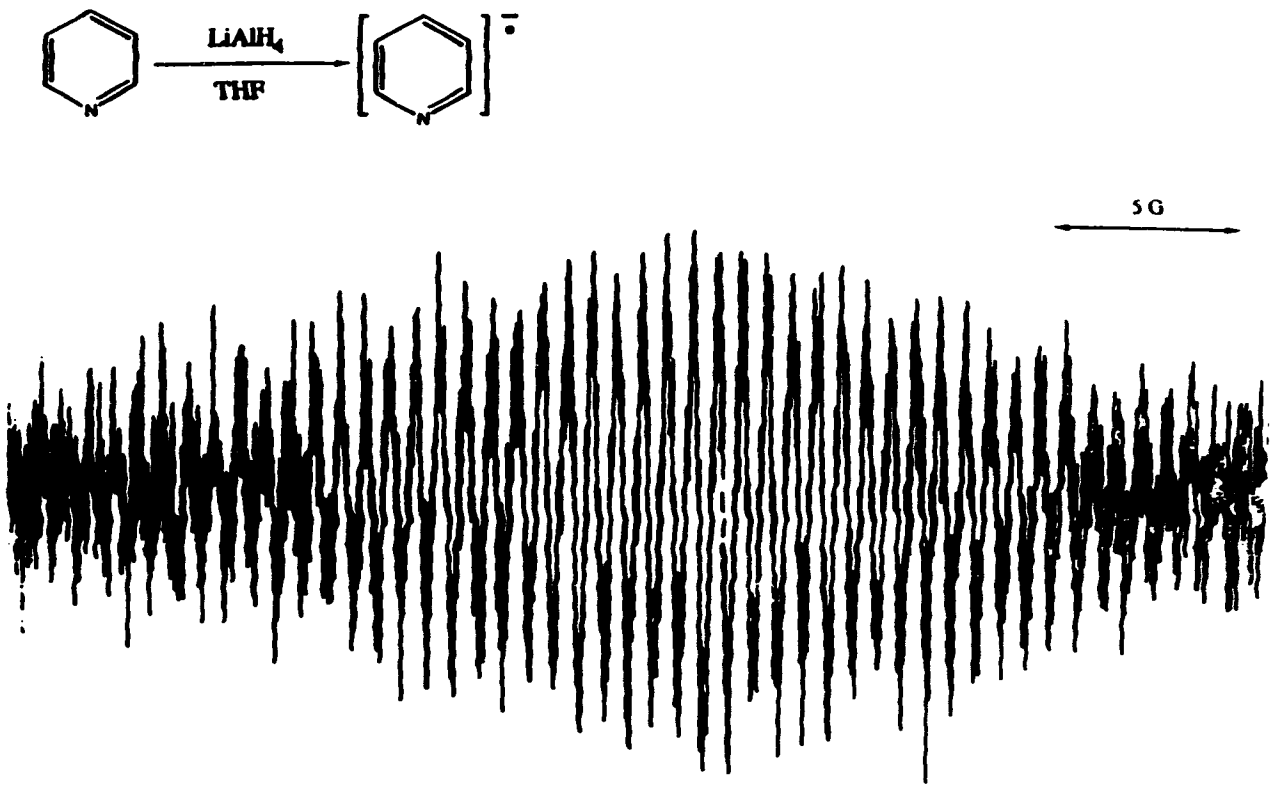
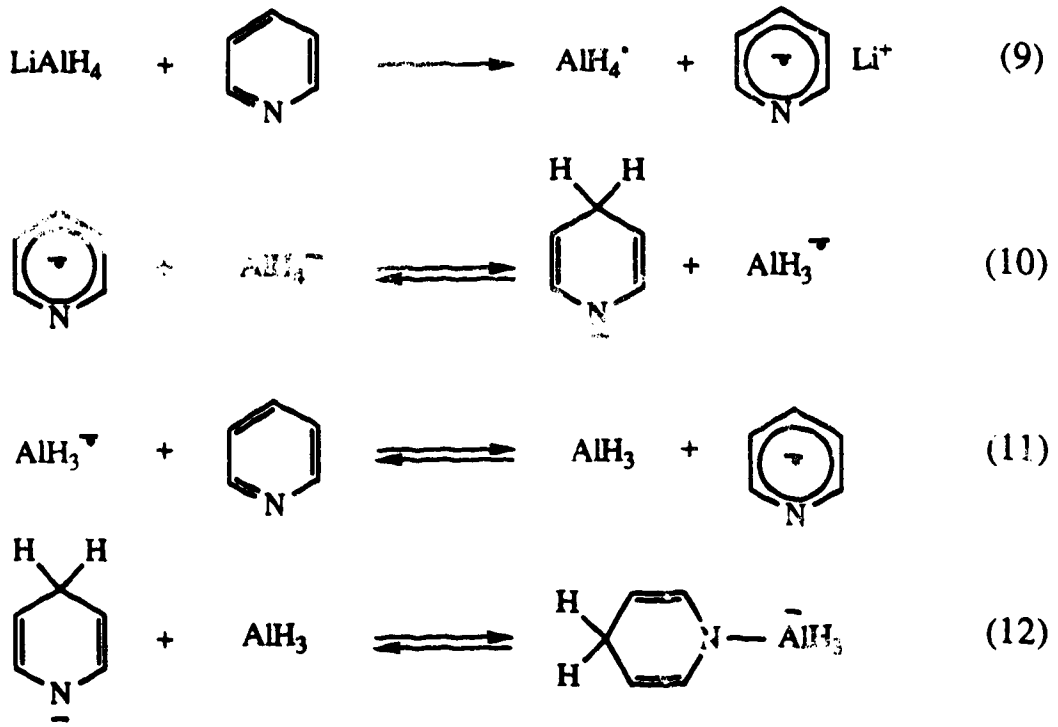


Fig. II-7. EPR Spectrum Obtained when LAH and Pyridine are Mixed at 23 °C.

The spectrum lasted for several hours at which time the ^{27}Al NMR showed that all of the LAH had reacted. The spectrum was identical to that of the electrochemically generated lithium salt of the radical anion of pyridine. The formation of the radical ion can be rationalized by invoking an electron transfer reaction between LAH and pyridine with the subsequent formation of the monodihydropyridyl complex, see Scheme II-3.



Scheme II-3

The mechanism which leads to further substitution after the LAH has all reacted may be either heterolytic (eqs 13-14) or homolytic (eqs 15-17), however at this time no further information is available. The stepwise addition of ligands was observed when the ^{27}Al NMR spectra were

monitored during the formation of LDPA. Five aluminate species are detected: LAH, mono-, di- and trisubstituted aluminum hydrides and LDPA, see Fig. II-8. The LDPA was formed at the expense of the hydride species.

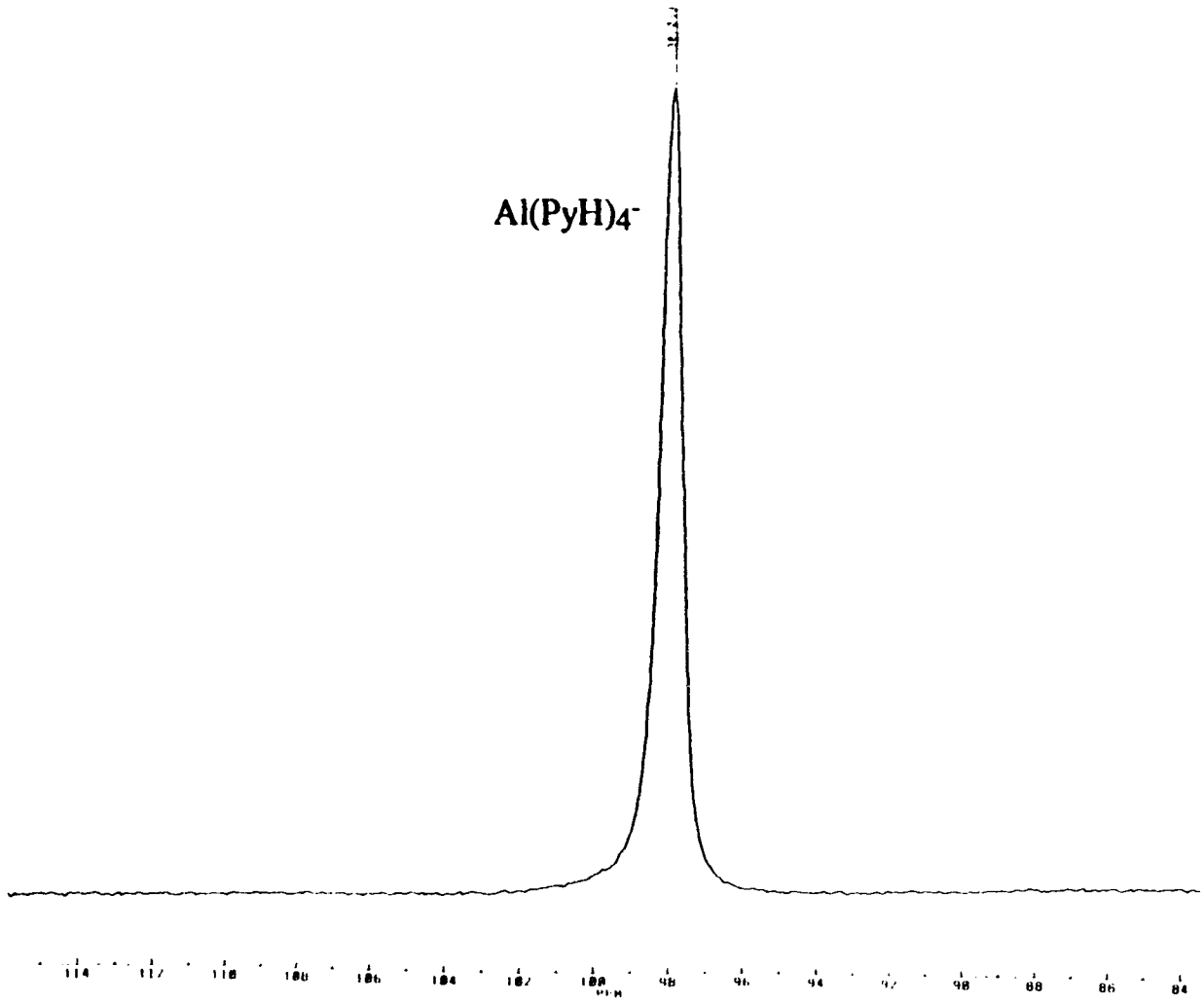


Fig. II-8. a) ^{27}Al NMR Spectrum of LDPA in Pyridine.

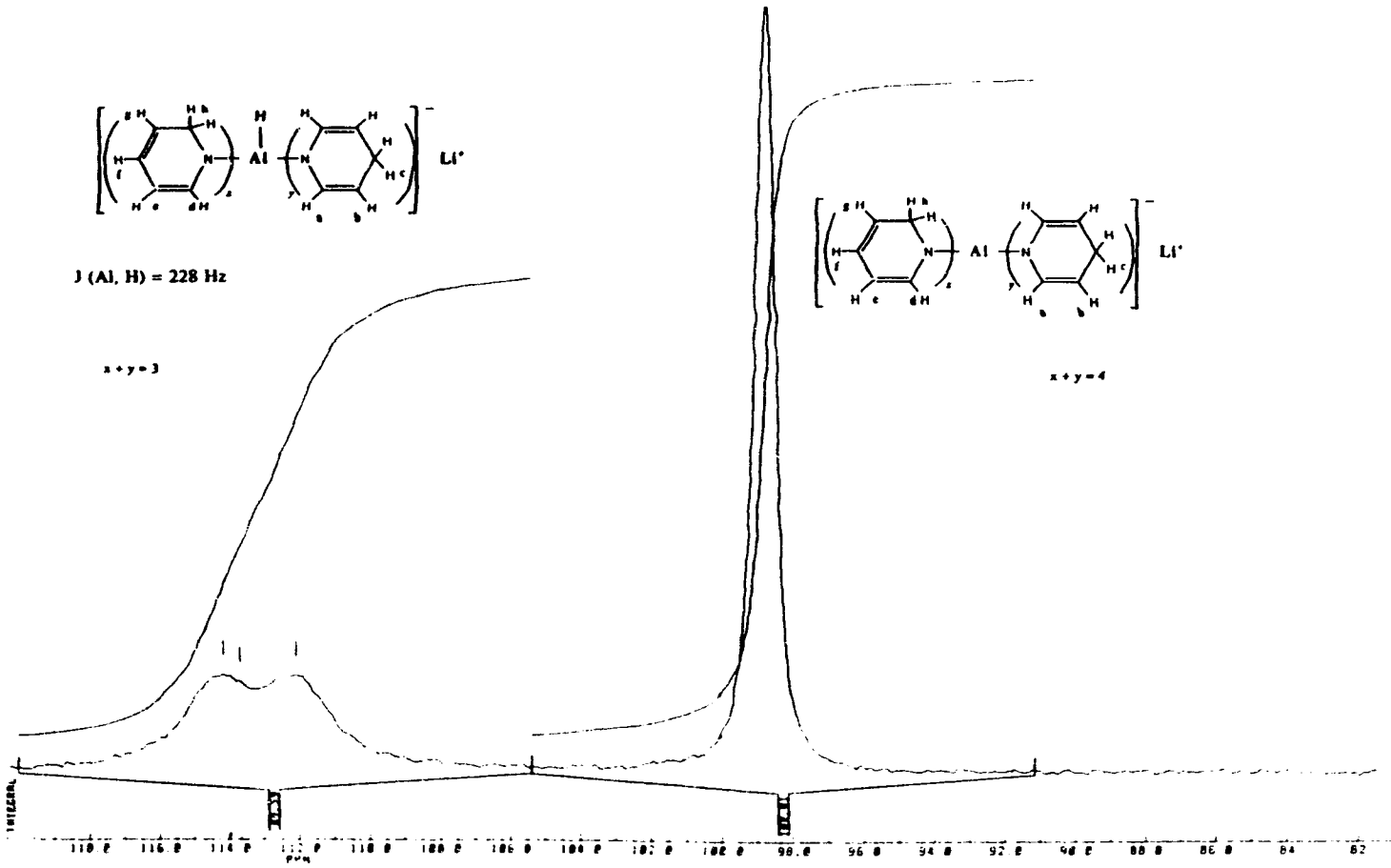


Fig. II-8. b) A ^{27}Al NMR Spectrum of LDPA Containing LiAl(PyH)3H in Pyridine (aged for less than 24 hours at r t).

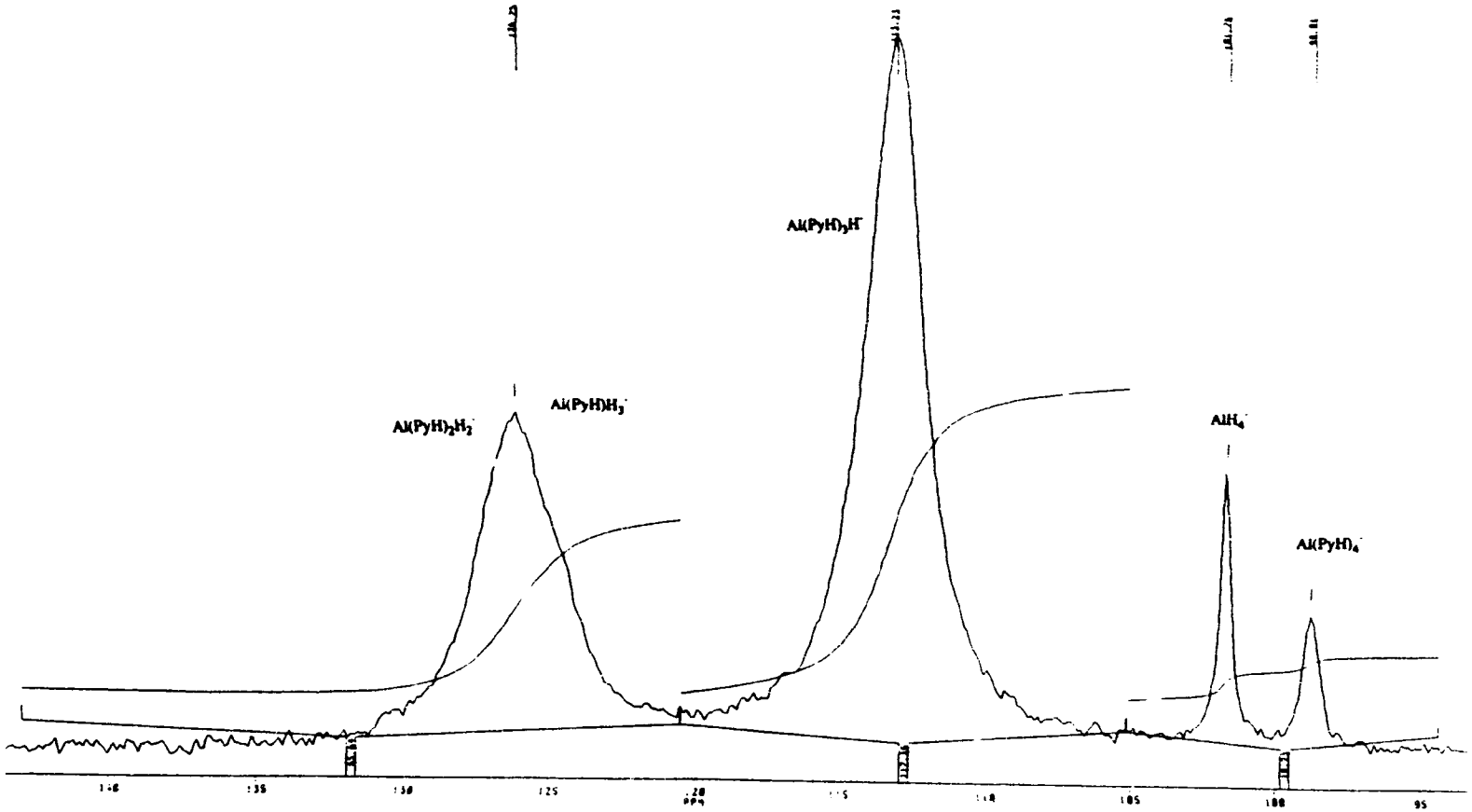
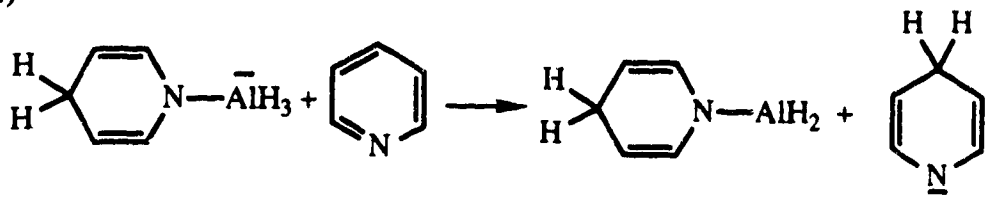
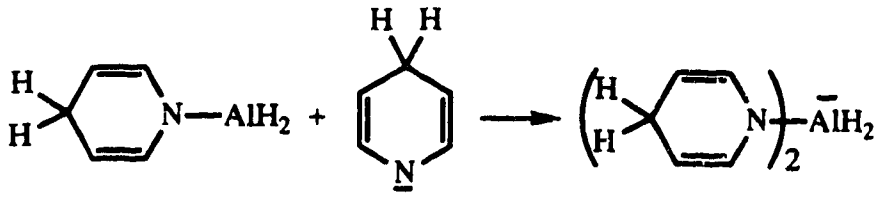


Fig. II-8. c) A ^{27}Al NMR Spectrum of a Pyridine Solution of LAH (5 hours after mixing of LAH with Pyridine at -30 °C).

a)



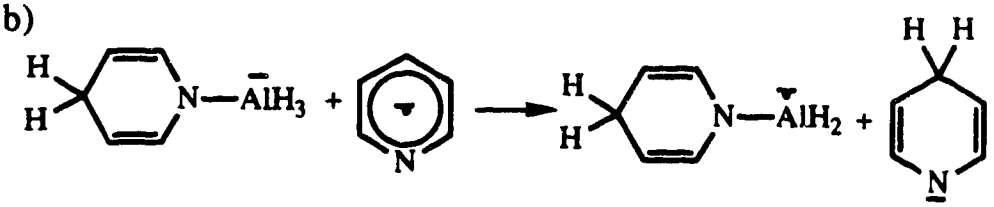
(13)



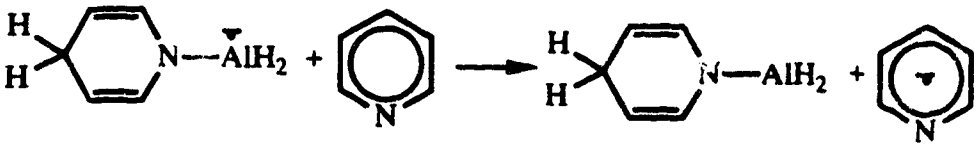
(14)

or

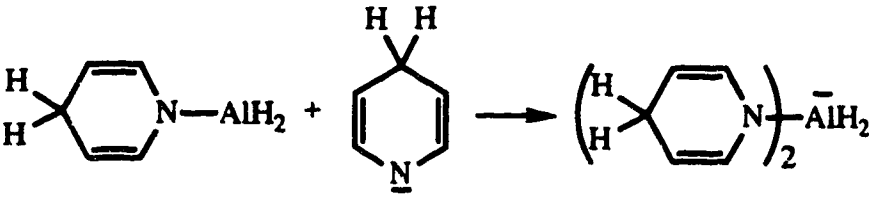
b)



(15)

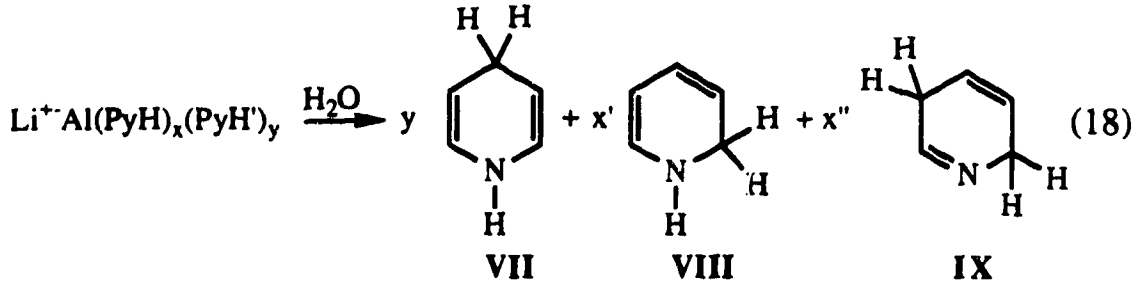


(16)



(17)

Hydrolysis of LDPA - When LDPA is treated with a small amount of water, in the absence of oxygen, the complex is hydrolyzed and a mixture of 1,4-, 1,2- and 2,5-dihydropyridines (**VII-IX**) is formed, eq 18.



(18)

Since in the LDPA complex only 1,2- and 1,4-dihydropyridyl ligands are present the formation of the 2,5-dihydropyridine presumably arises from the 1,2-dihydropyridyl ligand. This assumption was confirmed since the ratio of 1,4-/1,2-ligands (y/x) in LDPA is the same as the ratio of dihydropyridines, y/(x'+x"). Further confirmation of this assumption was obtained when the LDPA complex formed at 90 °C (>99% 1,4-dihydropyridyl ligands) was hydrolyzed; only 1,4-dihydropyridine was obtained (see Table II-4).

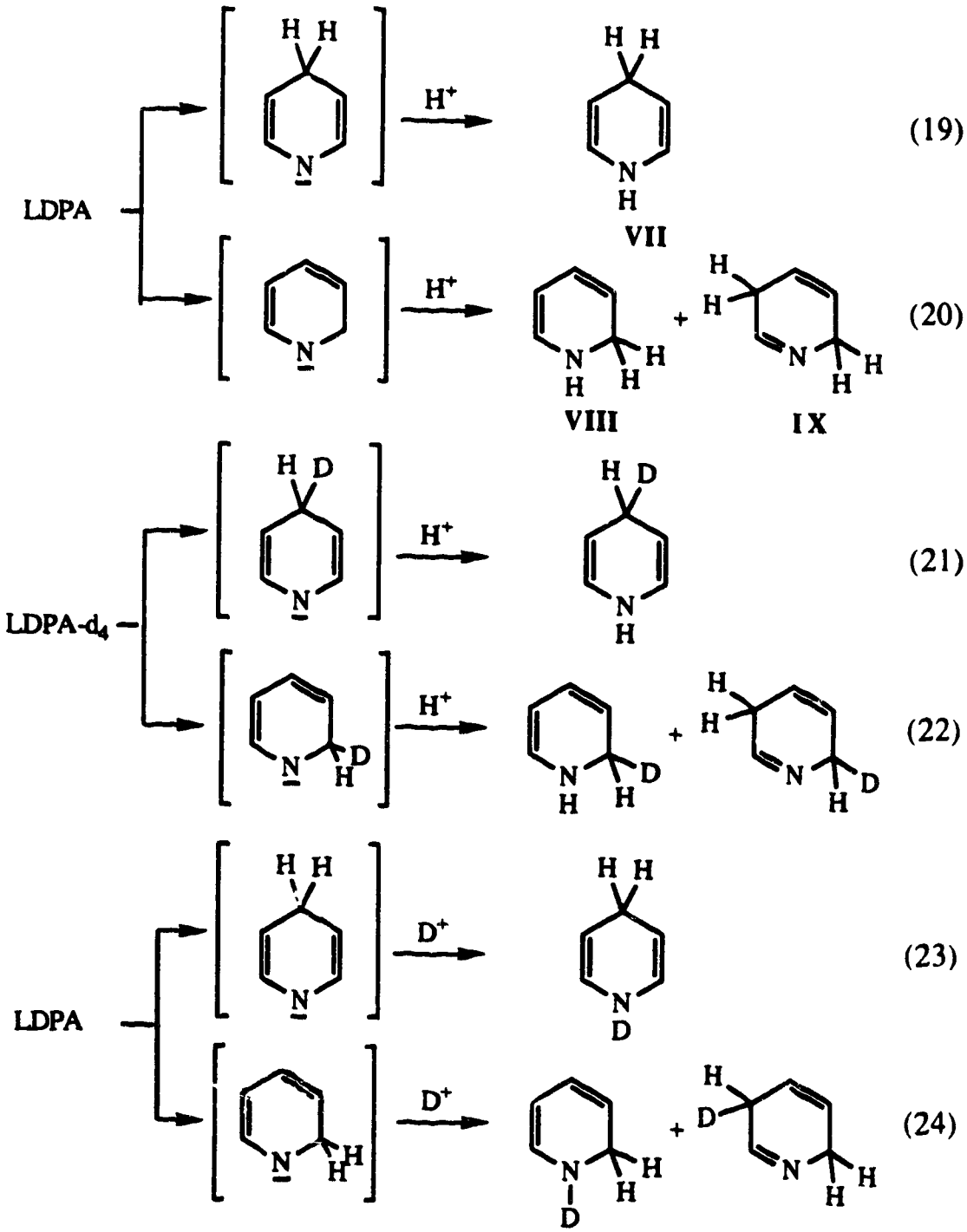
Table II-4. The Percentage of 1,4- and 1,2-Dihydropyridyl Ligands in LDPA before Hydrolysis and the Dihydropyridines Present in the Hydrolysate.

Sample No. Hydrolysis	Isomer	% Before Hydrolysis	% After
1	1,4	47.2	45.4
	1,2	52.8	29.0
	2,5	0.00	25.6
2	1,4	44.0	44.1
	1,2	56.0	27.1
	2,5	0.00	28.9
3	1.4	49.00	52.1
	1,2	51.00	24.0
	2,5	0.00	23.9
4	1,4	>99	100.0

The assignment of the structures for the three dihydropyridines (DHP's) was made on the basis of the ^{1}H 400 MHz and ^{13}C 100.6 MHz NMR spectra of the hydrolysis mixture, see Fig. II-9a and Fig. II-9b.

The assignment of the absorption in the mixture which was due to 1,4-dihydropyridine was confirmed by a comparison of its spectra (^{13}C and ^{1}H NMR) with the value reported in the literature.[6] Although the unsubstituted 1,2- and 2,5-dihydropyridines have not been previously reported, the assignments can be made from analysis of their ^{1}H and decoupled ^{1}H NMR spectra and their APT ^{13}C NMR (Fig. II-9b), see experimental sections. The assignment of the absorption of the 2,5-dihydropyridine was further confirmed by the observation of a NOE enhancement between adjacent protons at the 5- and 6-positions and the heteronuclear ^{13}C-^{1}H NMR chemical shift-correlation (HETCOR) spectrum of the dihydropyridines (**VII-IX**) (Fig. II-10). The spectra of the monodeuterated dihydropyridines were also in agreement with these assignments. When LDPA-d4 which was synthesized with LAD was hydrolyzed, monodeuterated 2-deutero-**VIII** and **IX** were formed as well as 4-deuterated-**VII** (eqs 21-22), see Fig. II-11. When LDPA was hydrolyzed with D_2O (eqs 23-24) 5-deutero-**IX** and N-deutero-**VII** and **VIII** could be detected, see Scheme II-4 and Fig. II-12a and Fig. II-12b.

The hydrolysis of the 1,4-dihydropyridyl ligand from LDPA leads only to 1,4-dihydropyridine while the 1,2-dihydropyridyl ligand yields only 1,2- and 2,5-dihydropyridines.



Scheme II-4

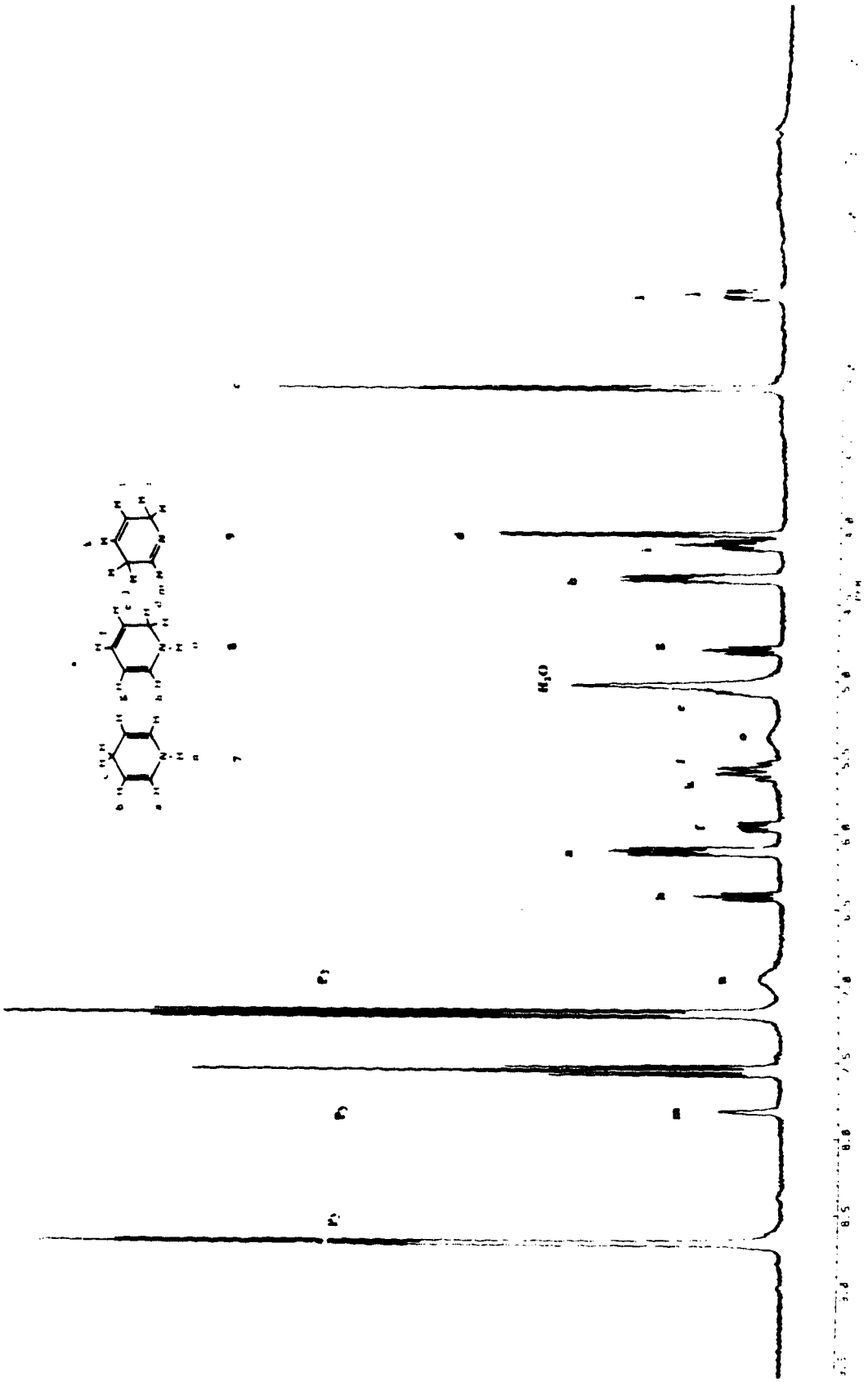


Fig. II-9. a) ^{1}H NMR Spectrum of the LDPA Hydrolysate in Pyridine-d5.

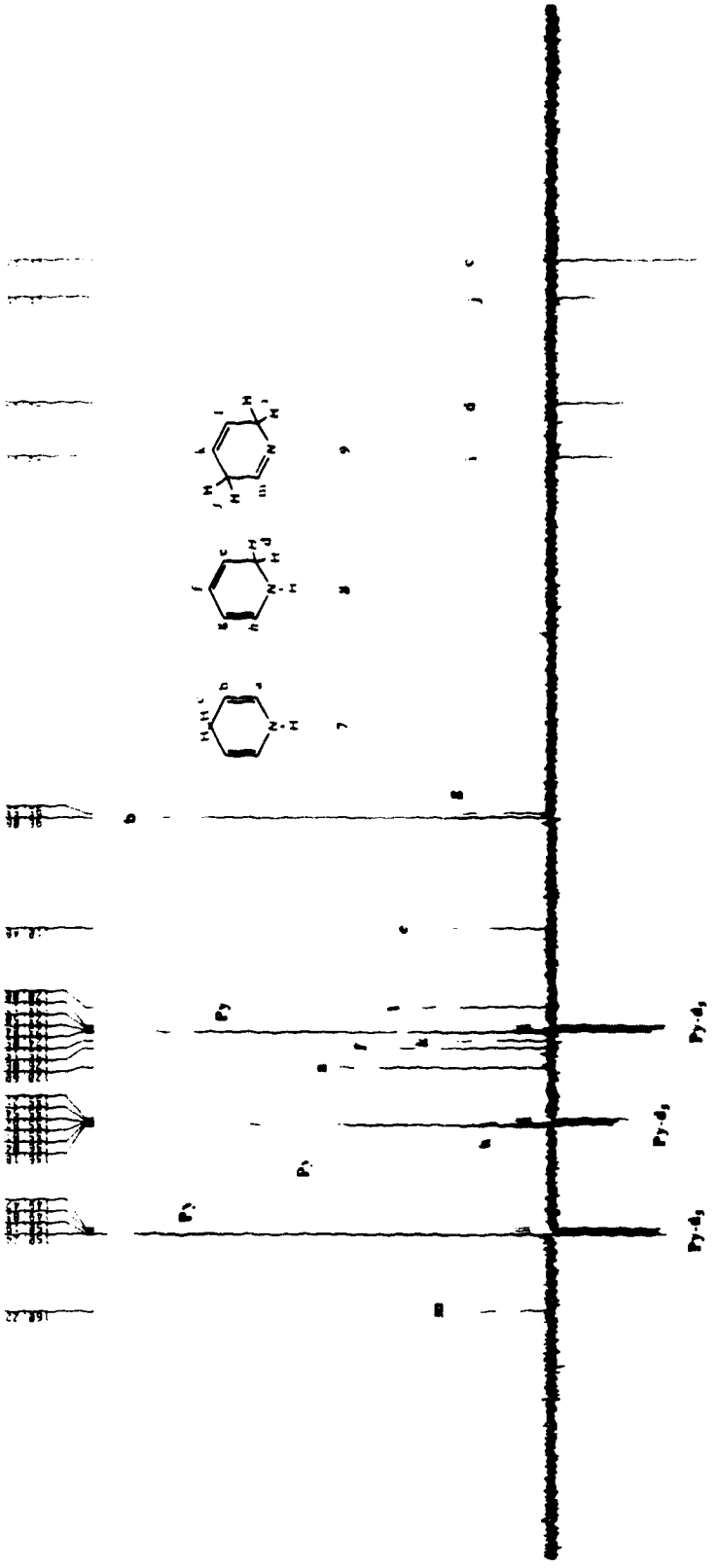


Fig. II-9. b) APT ^{13}C NMR Spectrum of the LDPA Hydrolysate.

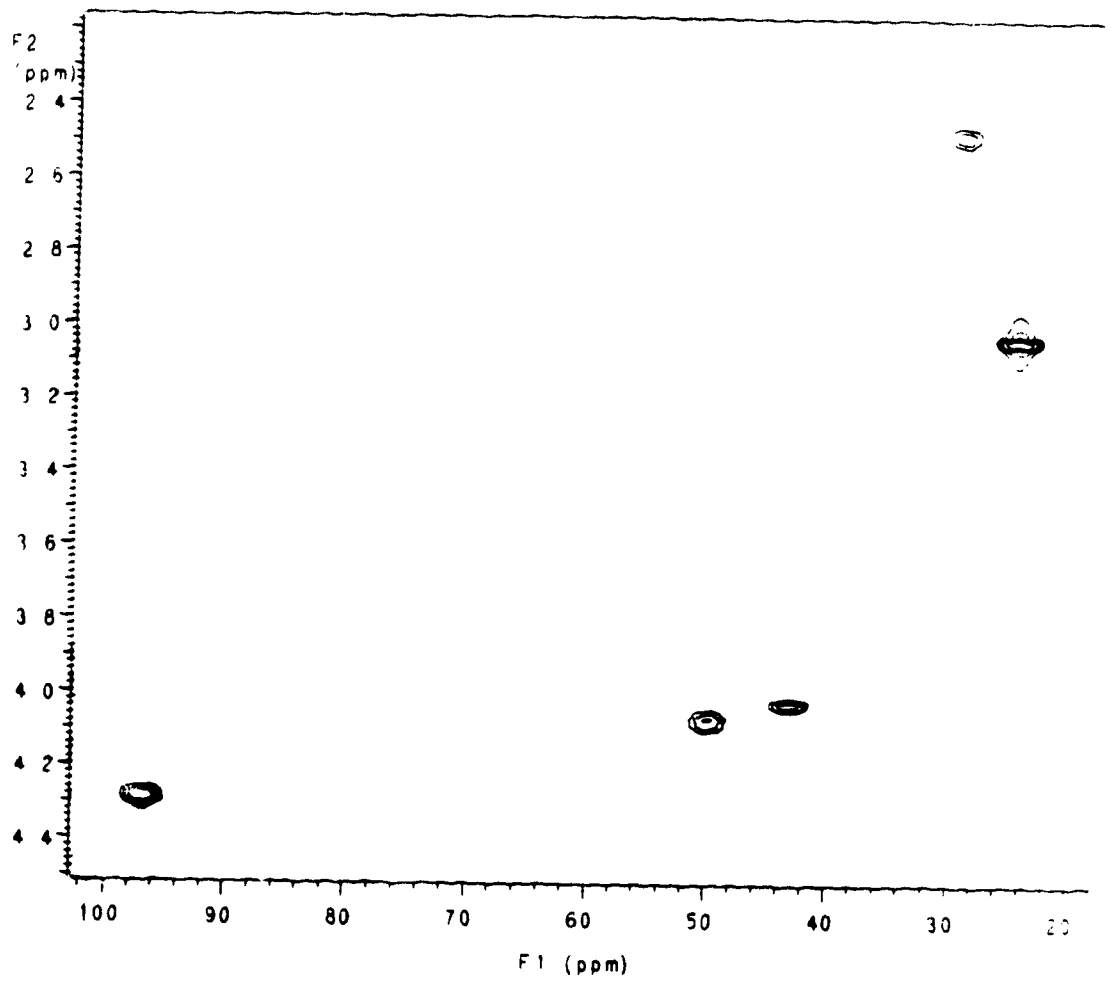


Fig. II-10. Heteronuclear ^{13}C-^{1}H NMR Chemical Shift-Correlation (HETCOR) Spectrum , of the Dihydropyridines (**VII-IX**) in the LDPA Hydrolysate in Pyridine-d5, Recorded at a ^{13}C Observation Frequency of 125.694 MHz (^{1}H 499.843 MHz). The Projected ^{13}C NMR Spectrum (20-100 ppm region) is Plotted Along the F1 axis, and the 2.2-4.5 ppm region from the Conventional ^{1}H NMR Spectrum is Plotted along the F2 axis.

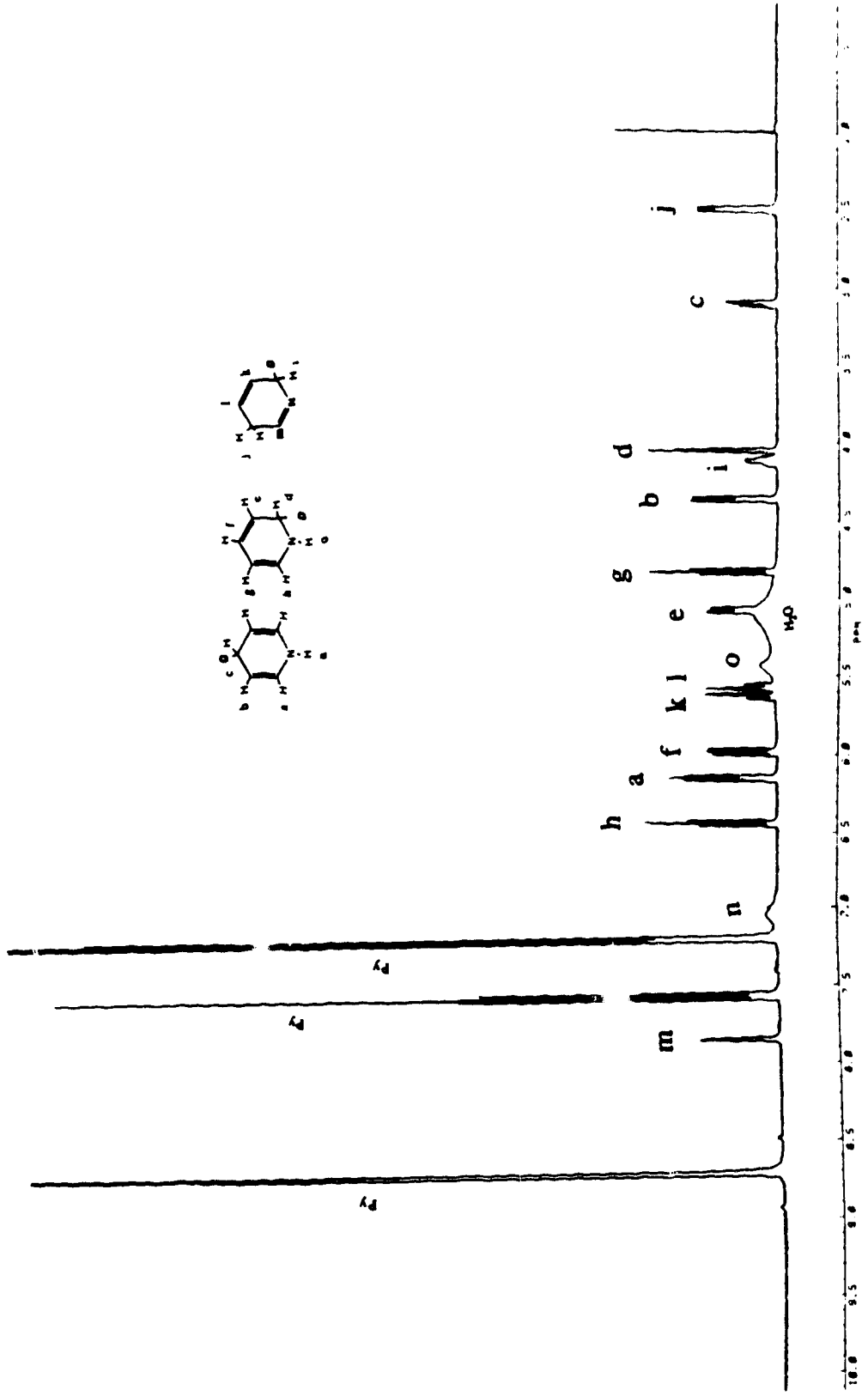


Fig. II-11. ^{1}H NMR Spectrum of the LDPA-d4 Hydrolysate in Pyridine-d5.

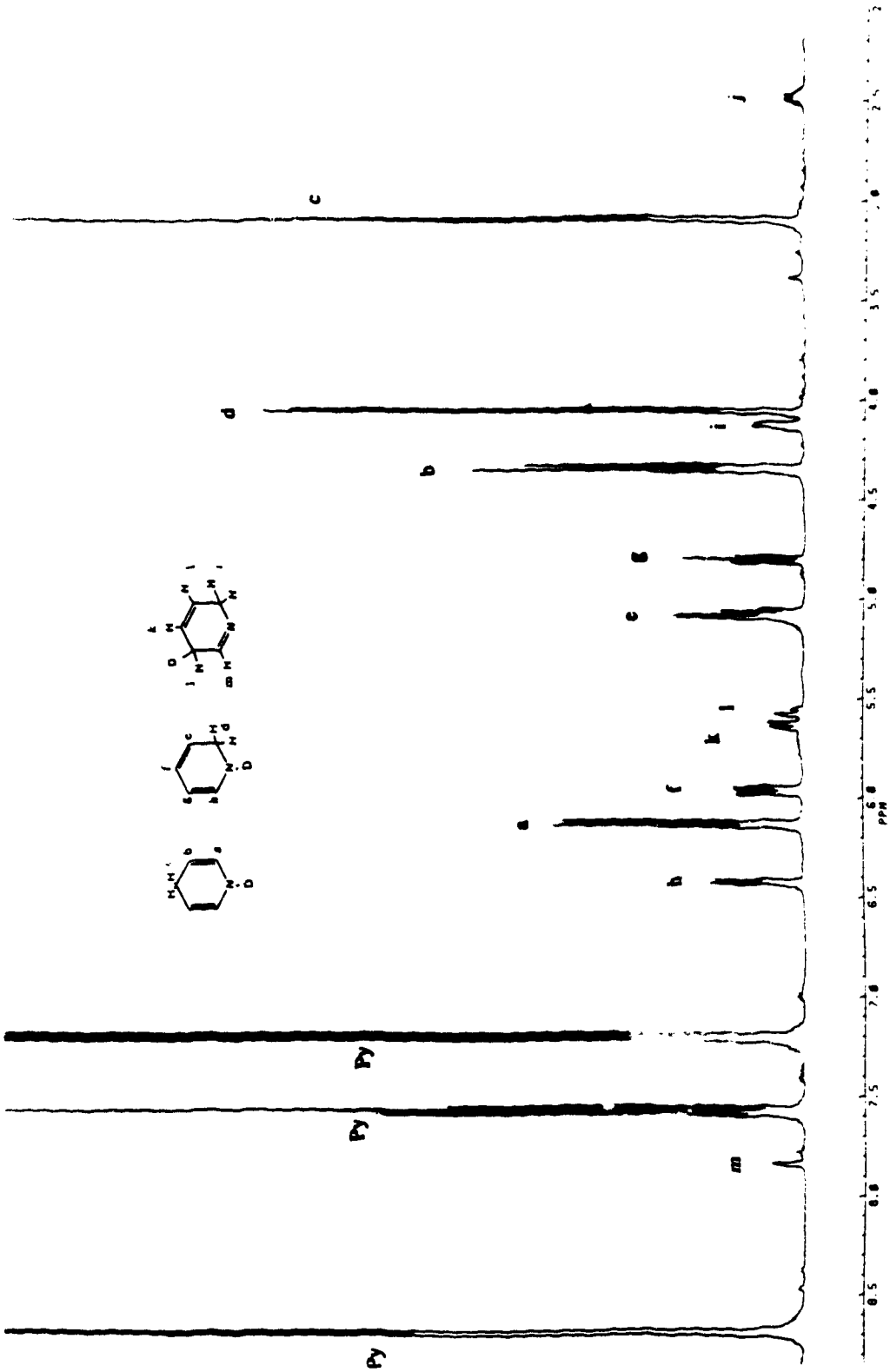


Fig. II-12. a) ^{1}H NMR Spectrum of the LDPA (D_2O) Hydrolysate in Pyridine-d5.

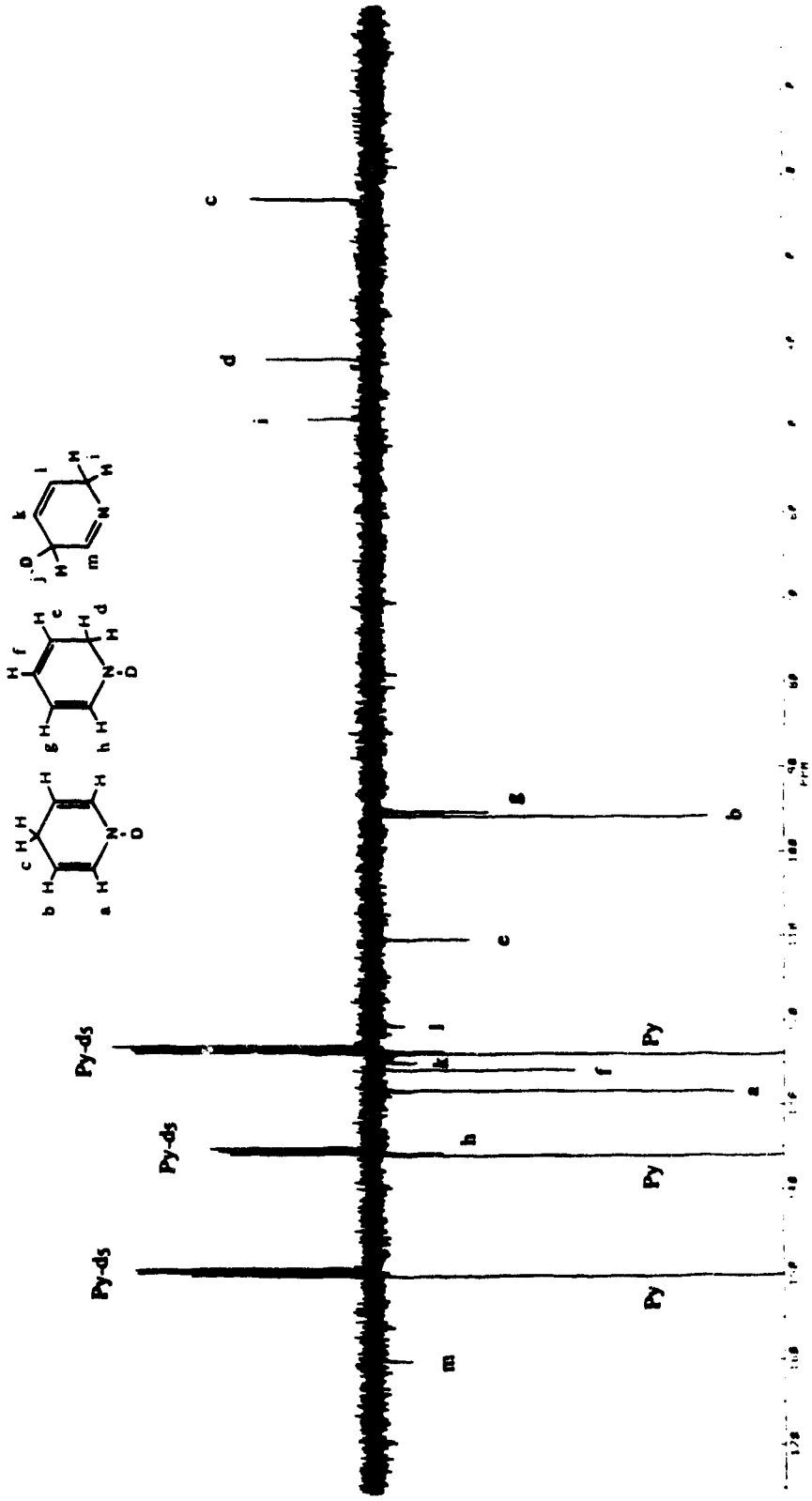


Fig. II-12. b) APT ^{13}C NMR Spectrum of the LDPA (D_2O) Hydrolysate.

Conclusions

The reaction of lithium aluminum hydride (LAH) and pyridine yields five lithium tetrakis(N-dihydropyridyl)aluminate (LDPA) isomers. The LDPA isomers are formed reversibly and contain both 1,2- and 1,4-dihydropyridyl ligands. The 1,2-dihydropyridyl ligands are incorporated as the products of kinetic control while the 1,4-dihydropyridyl ligands are formed as the thermodynamic products. When LDPA is synthesized using lithium aluminum deuteride and the deuterated LDPA is placed in pyridine solvent the ligands exchange with the pyridine in the solvent pool and form deuterated pyridine which is deuterated mainly in the 2- and 4-positions. A small amount of 3-deuterated pyridine is also detected. The formation of 3-deuteropyridine suggests that the pyridine radical anion is an intermediate present during the reaction of LAH with pyridine. In support of this suggestion when LAH and pyridine are mixed the EPR spectrum of the lithium salt of the pyridyl radical anion is observed. The stepwise addition of ligands to form LDPA is observed (NMR). Five aluminate species are detectable (^{27}Al NMR): LAH, mono-, di- and trisubstituted aluminum hydride and LDPA. The hydrolysis of LDPA in pyridine-d5 solvent yields a mixture of 1,4-, 1,2-, and 2,5-dihydropyridines. Both 1,2-, and 2,5-dihydropyridines are first obtained and characterized by this work.

Experimental

Materials - Pyridine (reagent grade, ACS) or **pyridine-d5** (99.5% D, Merck Sharp and Dohme Canada Limited) were stored over a mixture of BaO and KOH and were freshly distilled prior to use.

Lithium Aluminum Hydride ($LiAlH_4$) (General Intermediates of Canada) was purified by dissolving it in diethyl ether and separating it by filtering from insoluble LiH and solid $LiAlH_4$ was isolated from the clear solution by distillation.[2] **$LiAlD_4$** (Aldrich, 98 atom % D) was used as supplied.

Tetrahydrofuran (Aldrich, HPLC grade) was dried over KOH for >7 days and then distilled from sodium benzophenone ketyl before use. **THF-d8** (GIC, 99% D) was purified by the same method.

Instrumentation - The ^{1}H, ^{27}Al, and ^{13}C NMR spectra were obtained using a 400 MHz (Bruker) NMR spectrometer. All other spectra were obtained using a WH 200 MHz (Bruker) spectrometer.

The EPR spectra were obtained using a Bruker ER 200 E/SRC spectrometer fitted with a ER 4102 ST-Universal X-Band Resonator operated at 9.6 GHz. The *in situ* electrolysis was carried out in a degassed cells fitted with two Pt flag electrodes. The EPR spectrum from the mixture of LAH and pyridine was obtained by mixing the degassed reagents at room temperature in the EPR cell and immediately placing the cell in the cavity of the spectrometer and recording the spectrum.

General procedure for preparation of LDPA (I) - Purified LAH (0.200 g, 5.27 mmol) was added in small portions to a stirred aliquot, 20 mL, of freshly distilled pyridine. The pyridine was thermostated at the

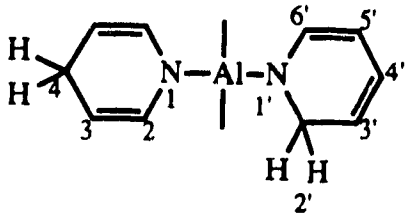
desired temperature before the addition of LAH. The addition was carried out under an atmosphere of dry nitrogen. After 24 h the reaction mixture was placed in a dry box under a nitrogen atmosphere, any unreacted solid was filter through sintered glass. The solutions were sealed in NMR tubes and again thermostated at the required temperature and periodically subjected to NMR analysis at that temperature.

When crystalline LDPA was desired a more concentrated pyridine solution of LDPA was prepared (0.5 M LAH). After filtering the unreacted LAH, light-yellow crystals were formed when the solution was allowed to stand at the desired temperature for 3-7 days. The crystals were filtered in a dry box and dried in vacuo over P_2O_5. ^1H NMR (400 MHz, THF-d8) δ 3.03~3.07 (m, 2 H, J_{34} = 3.21 Hz, J_{24} = 1.60 Hz, H-4)•y, 3.70~3.77 (m, 2 H, $J_{2'3'}$ = 4.41 Hz, $J_{2'4'}$ = 1.20 Hz, H-2')•x, 3.94~3.98 (m, 2 H, J_{23} = 8.20 Hz, J_{34} = 3.21 Hz, H-3)•y, 4.46~4.50 (m, 1 H, $J_{3'4'}$ = 9.02 Hz, $J_{2'3'}$ = 4.41 Hz, H-3')•x, 4.62~4.66 (m, 1 H, $J_{4'5'}$ = 5.01 Hz, $J_{5'6'}$ = 6.02 Hz, H-5')•x, 5.70~5.76 (m, 1 H, $J_{3'4'}$ = 9.02 Hz, $J_{4'5'}$ = 5.01 Hz, H-4')•x, 5.95~6.05 (m, 2 H, J_{23} = 8.20 Hz, J_{24} = 1.60 Hz, H-2)•y, 6.47~6.57 (m, 1 H, $J_{5'6'}$ = 6.02 Hz, H-6')•x; pyridine: δ 8.53, 7.76, 7.34 (free pyridine in THF-d8: δ 8.64, 7.68, 7.28).

^1H NMR (300 MHz, Py) δ 6.94~6.89 (m, H-6'), 6.62~6.54 (m, H-2), 6.12~6.04 (m, H-4'), 5.08~5.01 (m H-5'), 4.84~4.77 (m, H-3'), 4.34~4.25 (m, H-3), 4.24~4.18 (m, H-2'), 3.31~3.26 (m, H-4).

^{13}C NMR (100.6 MHz, THF-d8) δ 145.00 (C-6'); 135.53, 135.45 (C-2); 127.05, 127.02, 126.99, 126.96 (C-4'); 102.42, 102.32, 102.21, 102.11 (C-5' in **III-VI**); 96.45 (C-3'); 94.84 (C-3); 45.23 (C-2'); 24.91,

24.88, 24.85, 24.81 (C-4); pyridine: δ 150.40, 137.17, 124.85 (free pyridine in THF-d8: δ 150.79, 136.31, 124.38).



When deuterated LDPA was formed from LAD and pyridine the product showed deuterium in both the 2- position of 1,2-dihydropyridyl ligand and 4-position of the 1,4-dihydropyridyl ligands.

LiAl(PyD)4: ^{2}H NMR (Py, 30.7 MHz) δ 4.09 (^{2}H-4), 3.10 (^{2}H-2')(δ 8.53, 7.29, ^{2}H on pyridine-d_x); APT ^{13}C NMR (100.6 MHz, THF-d8) shows CHD (δ 44.85) and CHD (δ 24.44) (see Fig. II-13).

The crystalline material was transferred to a NMR tube in the absences of air or moisture (dry box, N_2 atmosphere). The proton absorption peaks were assigned from the decoupled spectra.

The above assignments would be confirmed by preparing a LDPA complex using LAH and Py-d5. The ^{1}H NMR of a Py-d5 solution of the LiAl (PyD5H)4 complexes showed ^{1}H absorption at δ 4.07 and 3.19.

^{27}Al NMR - The Reaction of $LiAlH_4$ with Pyridine. The Stepwise Formation of LDPA - A THF solution of pyridine (0.64 M) and LAH (0.13 M) was prepared under a nitrogen atmosphere at -30 °C. The ^{27}Al NMR (104.26 MHz) spectrum was taken and only the absorbance of LAH (δ 101.05, J_{Al-H} = 172.6 Hz, quintet, $[Al(H_2O)_6^{3+}]$ as external standard) (lit.[7a] 98.8 in THF, 97.7[7b], 100[7c]; J_{Al-H} = 175.5 Hz[7a], 172 Hz[7b], 175 Hz[7c]) was observed (15 min). The temperature was gradually

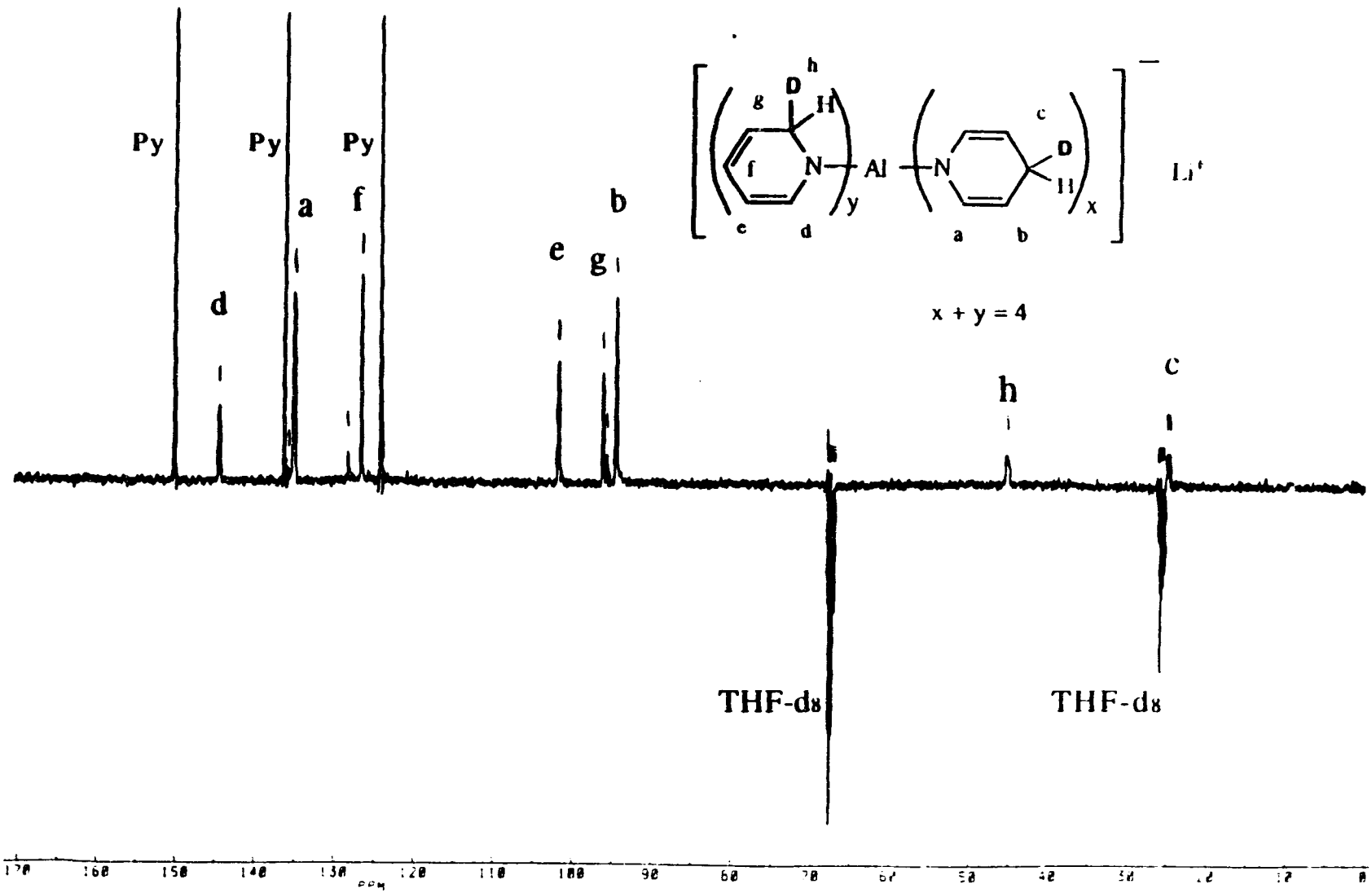


Fig. II-13. APT ^{13}C NMR Spectrum of the LDPA-d4 in THF-d8.

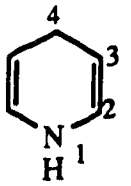
increased (20 min) to above room temperature (30 °C) and the formation of a product assigned to $LiAl(PyH)H_3$ appeared (d 125.07, broad multiplet). A new absorbance at d 124.97 (broad multiplet) became apparent after approximately 30 sec. The new absorbance was assigned to $LiAl(PyH)_2H_2$. After a subsequent 3 min the absorbance attributed to $LiAl(PyH)_3H$ began to appear (d 112.58, J_{Al-H} = 208.0 Hz, doublet), as the absorption of LDPA (d 98.8[illegible]nglet) appeared. The absorbance of LAH disappeared after 2.5 h. After 20 h only the absorbance of LDPA could be detected.

In an independent experiment carried out in an EPR tube, which was placed in the cavity of an EPR spectrometer, after the LAH has all reacted (~2.5 h) no EPR signal could be detected.

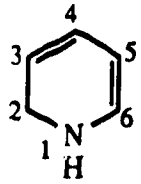
The Exchange Between Solvent Pyridine and the 4- and 2-Monodeuterated Dihydropyridyl Ligands in the LDPA Complex - A solution of $LiAl(PyD)_4$ was prepared from crystalline $LiAl(PyD)_4$ and dry pyridine at 23 °C. An aliquot portion of the solution was placed in a NMR tube which was then degassed and sealed. The ^2H NMR spectrum was recorded. A small amount of deuterated pyridine occluded in the crystalline material was initially observed. The tube was thermostated at 90 °C for 4 or 7 days and its ^2H NMR spectra were periodically recorded. The distribution of ^2H in the mixture is given in Table II-3.

The deuterated LDPA was prepared in the same manner as the protiated material but from LAD. The ^2H and ^{13}C NMR absorption resonances were assigned by analogy to the ^1H and ^{13}C NMR spectra of LDPA.

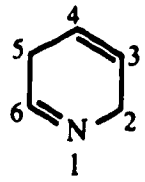
Hydrolysis of LDPA - Crystalline LDPA (0.050 g, 1.49 x 10^{-4} mol) dissolved in dry pyridine-d5 (0.50 mL) was placed in a NMR tube and H_2O (approximately 0.013 mL, 6.9 x 10^{-4} mol) was added. The hydrolysis was carried out under a nitrogen atmosphere. The tube was degassed and sealed and NMR (^1H and ^{13}C) spectra were taken (see Fig. II-9). The identities of the DHP's, **VII-IX**, were assigned to the individual compounds on the basis of their ^1H NMR integrated intensities and the structure for each compound was assigned by a consideration of the decoupled ^1H NMR and the APT ^{13}C NMR spectra.



VII



VIII



IX

The APT ^{13}C spectra of the mixture showed four methylene carbons, one each for **VII** and **VIII** and two belonging to **IX**.

1,4-Dihydropyridine, VII, (1,4-DHP) - ^1H NMR (400 MHz, Py-d5) δ 7.01-6.95 (b, N-H), 6.16-6.10 (m, 1H, J_{23} = 8.02 Hz, J_{24} = 1.50 Hz, J_{12} = 4.45 Hz, H-2), 4.37-4.34 (m, 1H, J_{23} = 8.02 Hz, J_{34} = 3.27 Hz, H-3), 3.12-3.08 (m, 1H, J_{34} = 3.27 Hz, J_{24} = 1.50 Hz, H-4).

^{13}C NMR (100.6 MHz, Py-d5) δ 128.62 (C-2), 96.11 (C-3), 22.3 (C-4). The chemical shifts obtained for **VII** were consistent with the 100 MHz value previously reported for 1,4-dihydropyridine[6a] (lit.[6a], ^1H NMR (100 MHz, Py-d5) δ 5.87, 4.24, 2.98; ^1H NMR (100 MHz, C_6D_6) δ 5.73, 4.42, 3.15; ^{13}C NMR (Py-d5, 25.1 MHz) δ 127.3, 95.3, 22.3).

1,2-Dihydropyridine, VIII, (1,2-DHP) - ^{1}H NMR (400 MHz, Py-d5) δ 6.44-6.40 (m, 1H, J_{16} = 5.65 Hz, J_{56} = 7.05 Hz, J_{36} = 1.00 Hz, J_{46} = 1.25 Hz, H-6), 6.00-5.95 (m, 1H, J_{34} = 9.35 Hz, J_{45} = 5.51 Hz, J_{24} = 1.50 Hz, J_{46} = 1.25 Hz, H-4), 5.38 (b, 1H, J_{16} = 5.65 Hz, J_{13} = 1.00 Hz, J_{12} = 1.70 Hz, J_{15} = 1.35 Hz, N-H), 5.10-5.05 (m, 1H, J_{23} = 3.95 Hz, J_{34} = 9.35 Hz, J_{13} = 1.00 Hz, J_{35} = 1.50 Hz, J_{36} = 1.00 Hz, H-3), 4.84-4.78 (m, 1H J_{45} = 5.51 Hz, J_{56} = 7.05 Hz, J_{35} = 1.50 Hz, J_{51} = 1.35 Hz, H-5), 4.07-4.04 (m, 1H, J_{23} = 3.95 Hz, J_{24} = 1.50 Hz, J_{21} = 1.70 Hz, H-2).

^{13}C NMR (100.6 MHz, Py-d5) δ 136.20 (C-6), 125.19 (C-4), 110.48 (C-3), 95.54 (C-5), 42.25 (C-2).

The high field H-2 proton (δ 4.07) of **VIII** couples to the NH and H-3 protons. The chemical shift of H-2 was similar that of N-phenyl-1,2-dihydropyridine (δ 4.26, H-2)[6b] and H-2 of the LDPA (1,2-dihydropyridyl ligand, δ 4.24 in pyridine). The chemical shifts of the remaining protons in **VIII**, were assigned from the decoupled ^{1}H NMR spectra. The APT ^{13}C NMR absorption of C-2 in the 1,2-DHP (**VIII**) (δ 42.25) was similar to the chemical shift of C-2 of the 1,2-dihydropyridyl ligand of **I** (δ 45.21).

2,5-Dihydropyridine, IX, (2,5-DHP) - ^{1}H NMR (400 MHz, Py-d5) δ 7.85 (m, 1H, J_{56} = 0.5 Hz, J_{26} = 0.8 Hz, H-6), 5.66-5.55 (AB quartet, 2H, J_{34} = 10.8 Hz, J_{45} = 3.1 Hz, J_{35} = 2.0 Hz, J_{32} = 2.5 Hz, J_{24} = 1.5 Hz, both lines of the downfield doublet appear as a broad multiplets, and both lines of the upfield doublet appear as multiplets, H-3,4), 4.13 (tm, 2H, J_{23} = 2.5 Hz, J_{25} = 8.0 Hz,J_{24} = 1.5 Hz, H-2), 2.49 (tm, 2H, J_{35} = 2.0 Hz, J_{45} = 3.1 Hz, J_{56} = 0.5 Hz, H-5).

^{13}C NMR (100.6 MHz, Py-d5) δ 160.13 (C-6), 126.08 (C-4), 120.82 (C-3), 49.27 (C-2), 28.26 (C-5).

When D_2O was used to hydrolyze **I**, the ^1H NMR spectrum assigned to **IX** changed. The H-3 doublet of multiplets at δ 5.55 became simpler since the coupling with one of the H-5 was removed. The H-2 absorption at δ 4.12 changed from a (1:2:1) triplet of multiplet to a (1:1) doublet of multiplets. The signal at δ 2.50 was diminished by one proton.

When LDPA was synthesized with LAD, after hydrolysis with H_2O, the spectrum assigned to **IX** changed. The intensity of the signal at δ 4.12 assigned to H-2 was diminished by one proton and the H-5 signal at δ 2.50 was reduced to a doublet. Irradiation at δ 2.50 (H-5) changed the signal at δ 4.12 to a complex singlet.

EPR Spectroscopy of a Mixture of LAH and Pyridine - Two separate THF solutions, one of pyridine (4 mL, 0.55 M) and one of LAH (0.5 mL, 1.60 M), were placed in the divided arms of a H tube containing an EPR sidearm. The solutions were degassed, sealed, mixed, and immediately placed in the cavity of the EPR spectrometer and an EPR spectrum was taken. A strong EPR signal was observed (54 lines, g = 2.0026). The same EPR spectrum was obtained when pyridine was allowed to react with LAD.

The Electrolytic Reduction of Pyridine - A THF solution of pyridine (0.5 M) and dry $LiClO_4$ (0.5 M) was electrolyzed in a degassed EPR cell. The EPR spectrum of the radical anion of pyridine (Li^+ $Py^{\bullet-}$) was recorded.[8] The spectrum was identical to that recorded for the radical anion formed during the reaction of LAH with pyridine.

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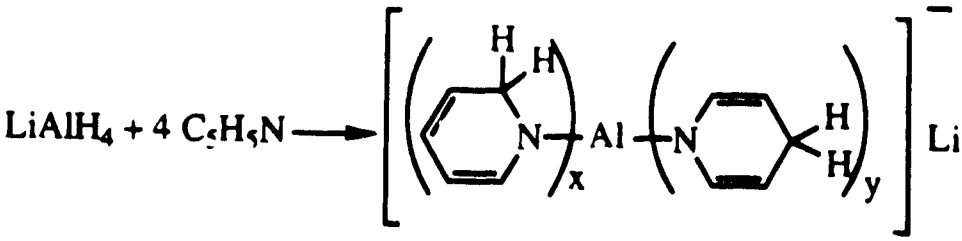
CHAPTER 3

The Use of Chemical Probes to Differentiate Between Polar and SET-Hydrogen Atom Abstraction Pathways Involved in the Reduction Reaction Promoted by an 8-Al-4 Anion[1,2]

Introduction

A number of years ago, Lansbury and co-workers reported that a pyridine solution of $LiAlH_4$ (LAH) formed a 1:4 molecular complex, lithium tetrakis(N-dihydropyridyl)aluminate (LDPA), **I**, see eq 1.[3,4]

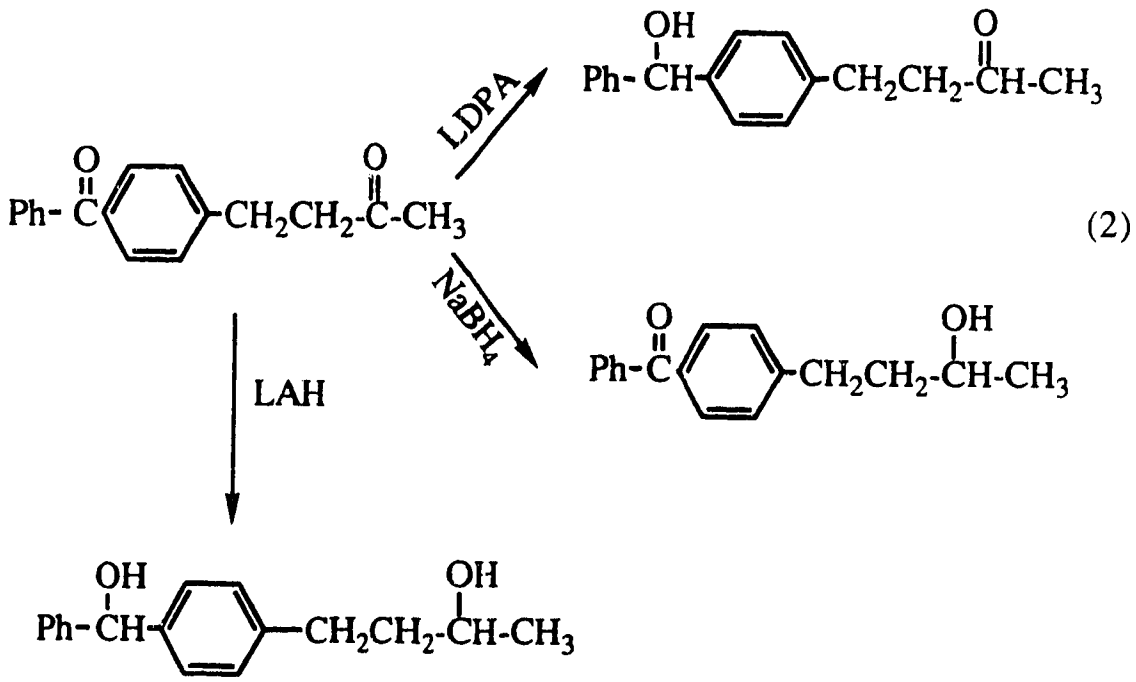


(1)

I

$x + y = 4$

The newly formed reagent is less reactive than LAH when it was allowed to react with organic carbonyl containing substrates.[3] The reagent was more reactive with diaryketones than with aliphatic ketones, when its reactivity was compared to the reduction reactions of $NaBH_4$ (see eq 2).[3,5]

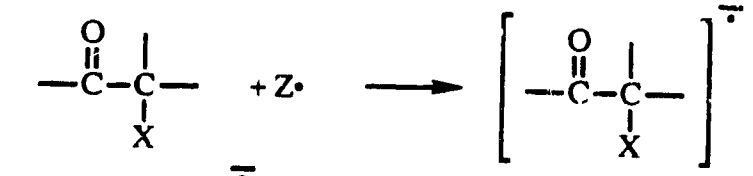


(2)

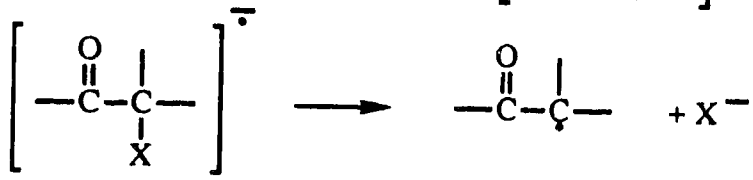
The reduction reactions of LDPA were reported to proceed by a polar mechanism in which a hydride is transferred to the substrate from either the 1,2- or 1,4-dihydropyridyl ligand.[5] It was reported that in the reduction of 4,4'-dichlorobenzophenone no significant difference in the reduction rates was observed from either the 1,2- or 1,4-dihydropyridyl groups in LDPA.[5]

Recently LDPA has been proposed as an inorganic analog of the dihydropyridyl moiety of NADH or NADPH.[1] Since model compounds containing the 1,4-dihydropyridyl function have been shown to react by both homolytic[6,7] and heterolytic pathways[6,8] it is necessary to investigate in some detail the reduction reactions of LDPA. LDPA itself has been shown to undergo not only heterolytic reductions[5] but also to produce persistent radicals (EPR) by an electron transfer process.[9]

Homolytic



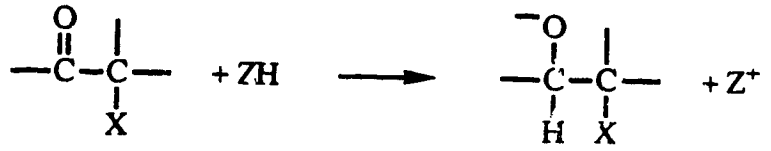
(3)



(4)

(5)

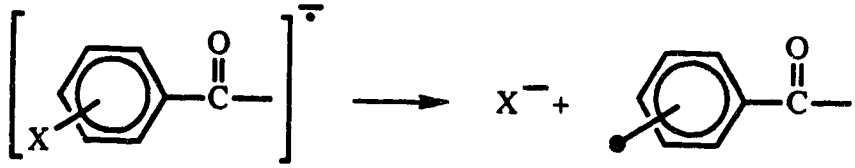
or **Heterolytic**



(6)

Homolytic

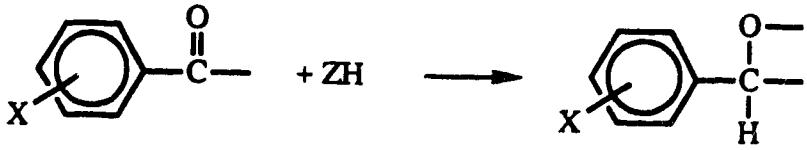
(7)



(8)

(9)

or **Heterolytic**



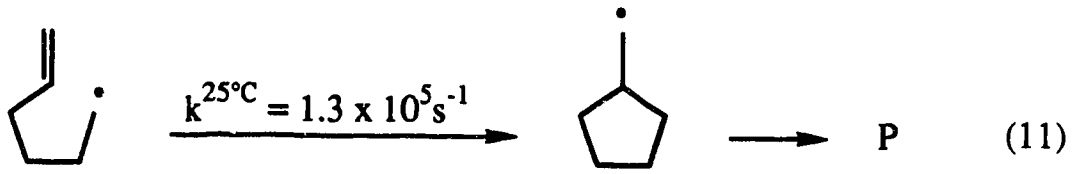
(10)

Scheme III-1

The use of EPR spectroscopy to differentiate between homolytic and heterolytic pathways has limitations since EPR active materials can be detected at a very low concentration (>10^{-7} M) and the observation of EPR spectra is not conclusively indicative of the major pathway involved in the reaction.

The use of α-haloketones[10,11] or ring substituted aromatic ketones[11] as mechanistic probes has been used successfully to differentiate between the reduction mechanisms which involve either homolytic electron transfer-hydrogen atom abstraction chain (eqs 3-5, 7-9) or a heterolytic hydride transfer pathway (eqs 6 or 10), Scheme III-1.

Another chemical probe used widely to differentiate between homolytic and heterolytic pathways is based on the cyclization of the 5-hexenyl radical, where products produced from the cyclopentylmethyl radical are indicative of a radical intermediate (eq 11).[12]



(11)

A preliminary report concerning the LDPA reduction of 5-hexenyl iodide stated that the cyclized hydrocarbon products that were formed are indicative of the involvement of a SET mechanism.[9] Unfortunately the results of this study have not been published and no details concerning the reduction are available.

Results and Discussion

A number of chemical probes are useful to establish the mechanism of LDPA reduction of aromatic ketones. When LDPA was allowed to react with benzophenone in an EPR tube no EPR spectra for benzophenone ketyl could be observed. With more hindered ketones, mesityl phenyl ketone (MPK) or dimesityl ketone (DMK), Ashby has reported that the ketyls of both aromatic ketones were almost immediately detected when the ketones were treated with LDPA.[9] Contrary to this report, when LDPA was allowed to react with either MPK or DMK, no EPR spectra could be detected within a few hours. Only after an extended period of time (MPK, 2 d; DMK, 5 d) was an EPR signal detectable. For DMK a signal of maximum intensity was observed after 24 d (Fig. III-1a) while with MPK maximum intensity is observed in 5 d. As previously reported[9] the spectra observed were identical to those of the independently generated lithium ketyls of MPK or DMK, however, the difference in the rates of formation of the radical ions from the aromatic ketones appears to be due to the method of preparation of LDPA. In the present work crystalline LDPA, free from LAH, was used to obtain the ketyl spectra. The spectra of the lithium ketyls could be immediately generated from treatment of each ketone with LAH (Fig. III-1b and Fig. III-2). An analysis of the reaction products from the reaction of the two ketones showed only alcohol is produced (DMK > 40 d) with LDPA. With LAH not only is the ketyl of DMK formed immediately but also after 24 h the spectrum of the radical ion had changed to that of the dimesityl methyl radical (Fig. III-3).[13] An

analysis of the product mixture showed that dimesityl methane had been produced, a product which is not formed from the LDPA reduction of DMK or dimesityl carbinol.

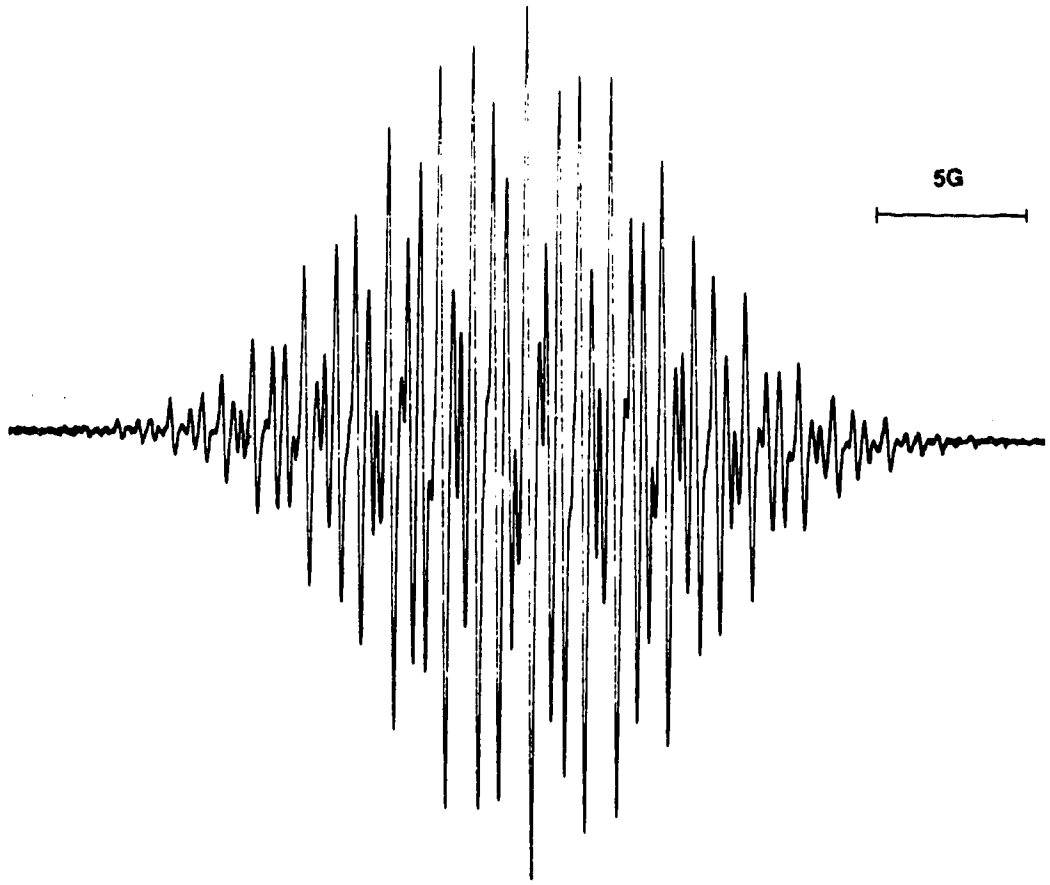


Fig. III-1a. EPR Spectrum Obtained from the Reaction of LDPA with DMK in THF.

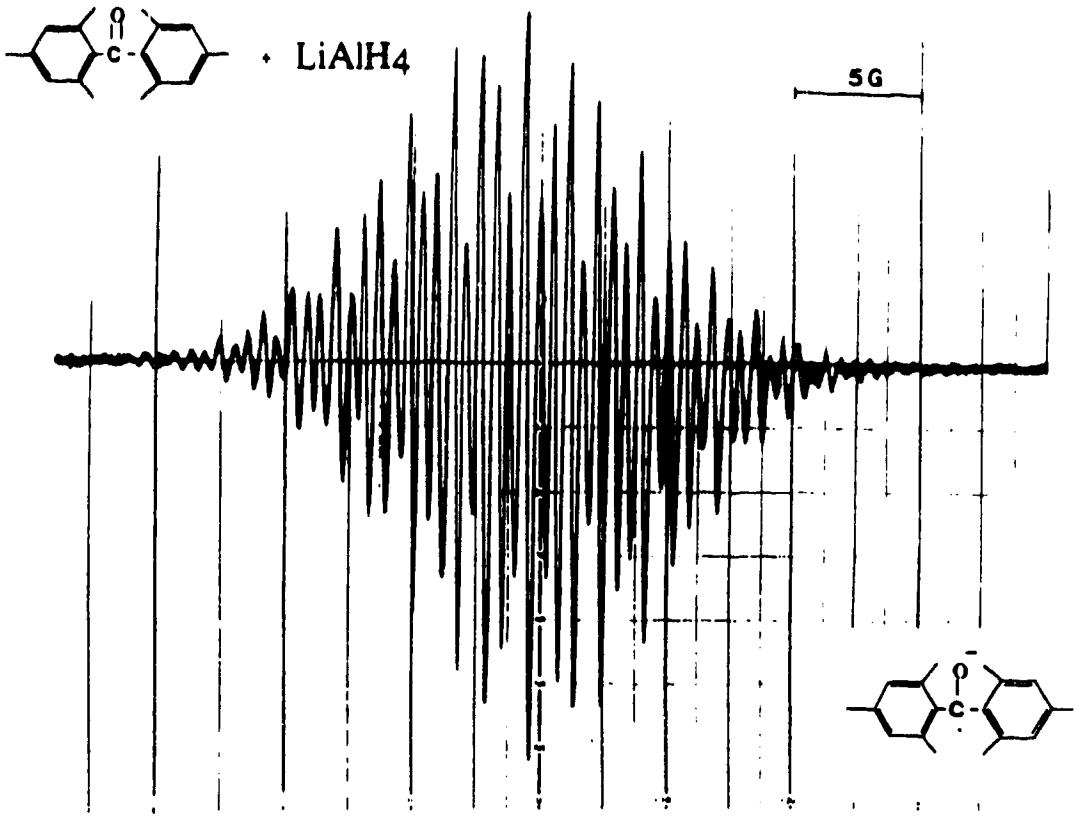


Fig. III-1b. EPR Spectrum Obtained from the Reaction of LAH with DMK within 24 h in THF.

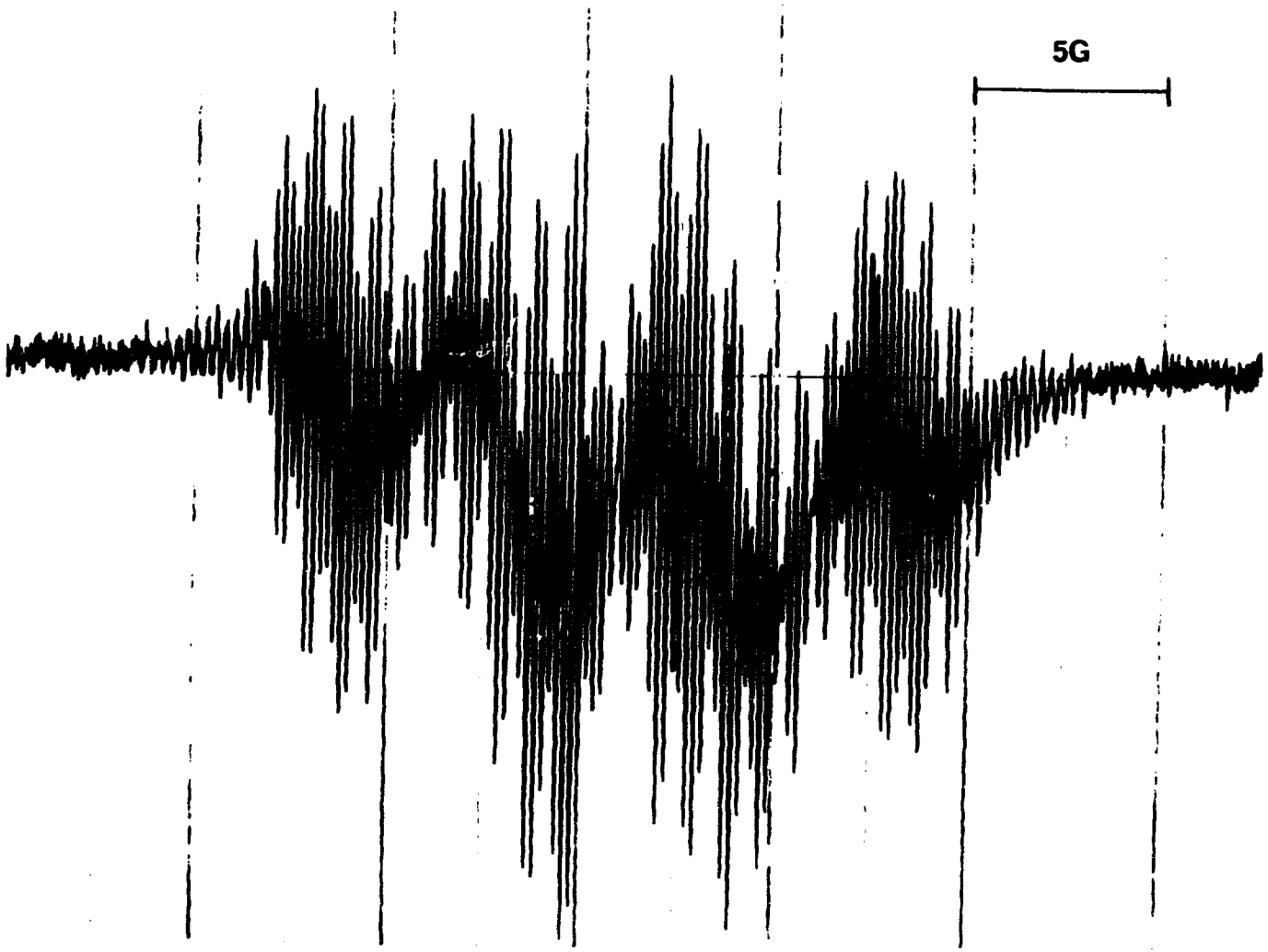
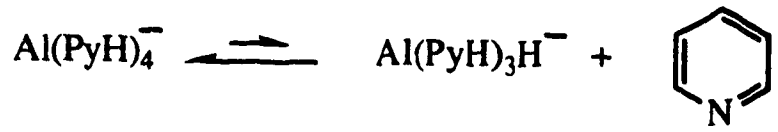


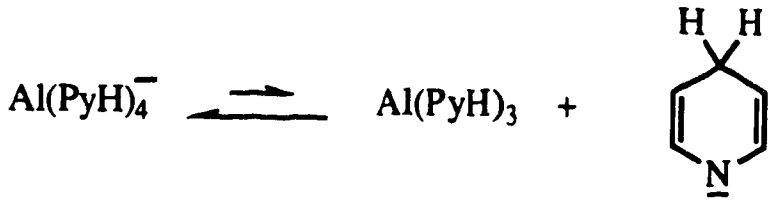
Fig. III-2. EPR Spectrum Obtained from the Reaction of LAH with MPK in THF.

Fig. III-3. EPR Spectrum Obtained from the Reaction of LAH with DMK after 24 h in THF.

From these results it appears that the LDPA reductions of DMK and MPK previously reported[9] were carried out with LDPA that was contaminated with LAH (insufficiently "aged") while the LDPA that was prepared free from LAH (^{27}Al NMR)[4] was much less reactive than LAH. Since the formation of LDPA is reversible,[4] it is not clear that the radical involved was a result of SET from LDPA, from another aluminate complex (eq 12) or from the dihydropyridyl anion (eq 13). Since the equilibrium lies far to the left, electron transfer to form a stable intermediate will be, as observed, extremely slow.



(12)



(13)

With very strong electron acceptors, most likely LDPA itself can act as an electron donor, since it rapidly reacts with either trityl bromide or 2,6-di-*t*-butylbenzoquinone to give the trityl radical (Fig. III-4) or the benzoquinone ketyl radical ion (see eqs 14-15 and 16) (Fig. III-5). When the reaction of trityl bromide was quenched after 6 h a 54% yield of triphenylmethane was obtained accompanied by a number of other minor products; no starting material could be detected.

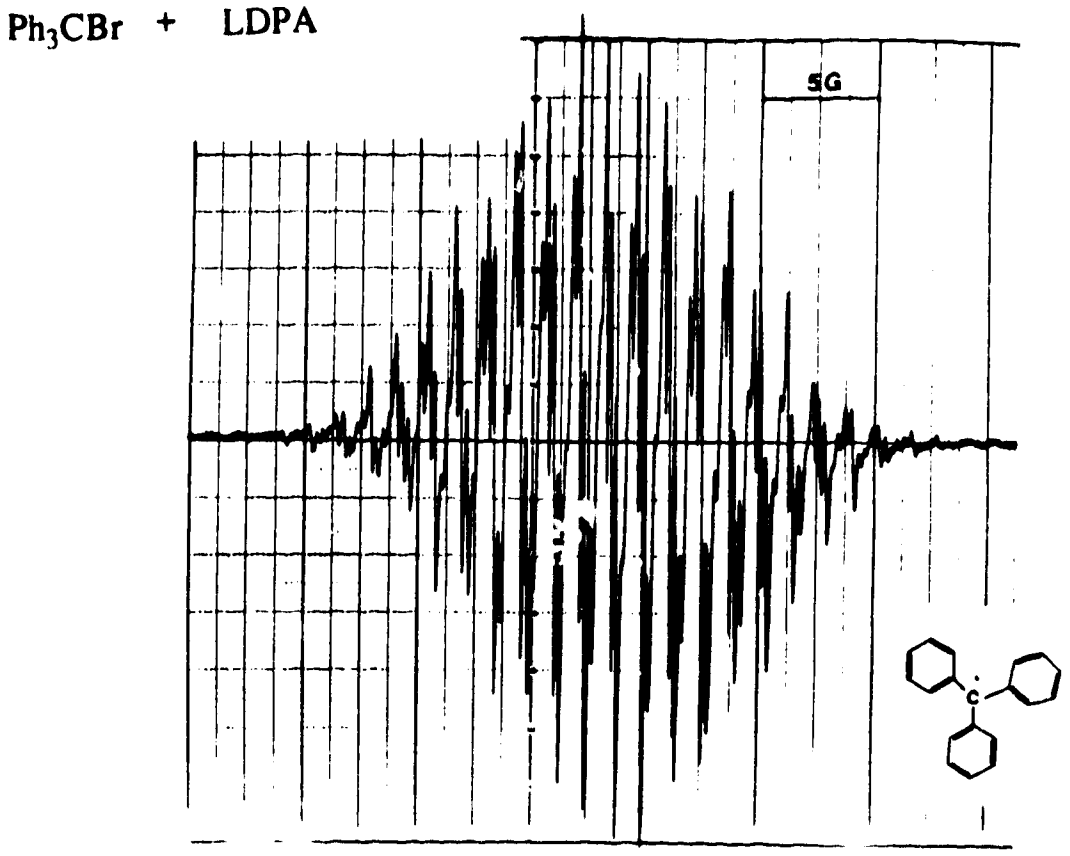


Fig. III-4. EPR Spectrum Obtained from the Reaction of LDPA with bromotriphenylmethane in THF.

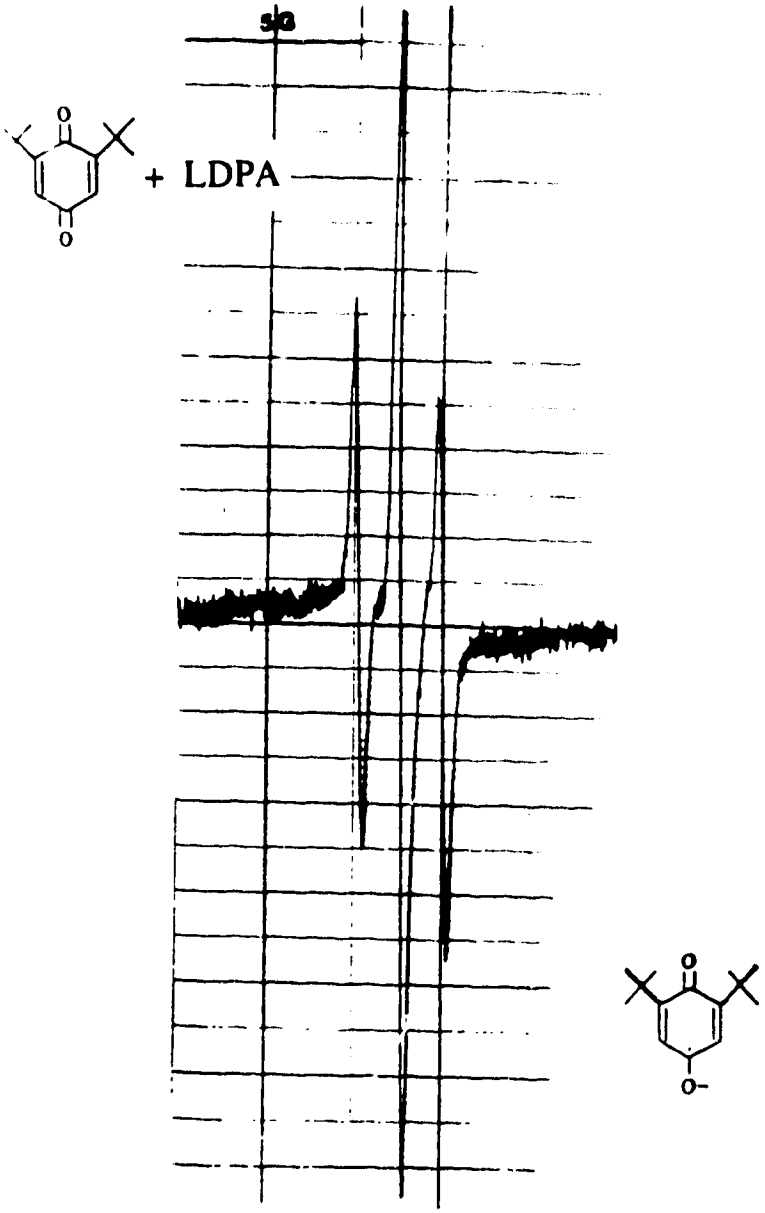
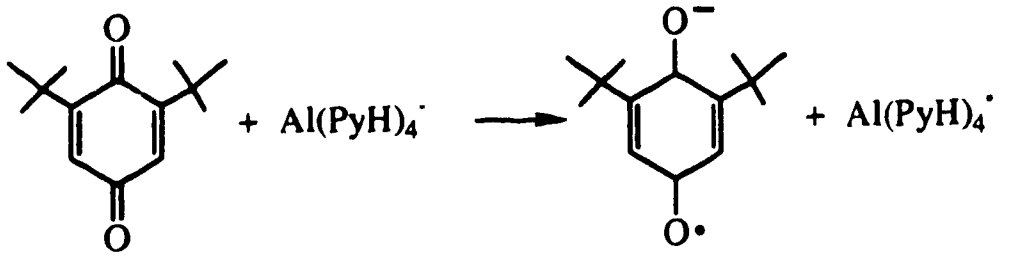


Fig. III-5. EPR Spectrum Obtained from the Reaction of LDPA with 2,6-di-*t*-butylbenzoquinone in THF.

$$Ph_3CBr \rightleftharpoons Ph_3C^+Br^- \quad (14)$$

$$Ph_3C^+ + Al(PyH)_4^- \longrightarrow Ph_3C\bullet + Al(PyH)_4^{\bullet} \quad (15)$$



(16)

Whether LDPA reacts by a SET or a hydride transfer mechanism ketone reductions are slower the more hindered the substrate. The steric effect appeared to be qualitatively true when LDPA was allowed to react with benzophenone, MPK, and DMK, see Table III-1.

Table III-1. Reduction of Diarylketones with LDPA in THF.[a]

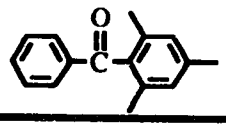
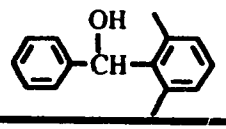
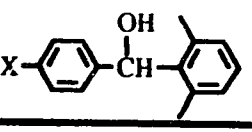
Ketone	[LDPA]/[ketone]	Condition	Yields, % (Carbinol)	Recovery of Ketone, %
Ph_2CO	1.25	23 °C, 3.5 h	97	none
PhCOMes	11.0	23 °C, 66 h	40.7	61.8
	11.0	61 °C, 66 h	98.8	1.1
Mes_2CO	11.3	23 °C, 10 d	0.0[b]	100
	11.3	61 °C, 66 h	14.3	85.0

[a] All the reactions were run in degassed H reaction tubes. [MPK] = 0.0178 M, [DMK] = 0.0129 M, [Ph_2CO] = 0.117 M.

[b] Quenched with benzophenone before quenched with water. When the products were analyzed on GC, it was shown that 4.0% of Ph_2CO was consumed to form 3-pyridyl diphenyl carbinol, the structure of which was confirmed by GC/MS and GC/IR upon comparison with authentic sample (prepared independently from methyl ester of nicotinic acid and 2 equivalents of lithiobenzene).

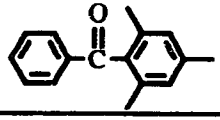
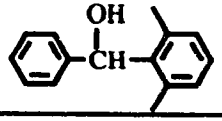
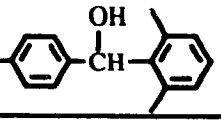
The Fragmentation Probe - When excess LDPA was allowed to react with 4'-bromoacetophenone (**II**) (23 °C or 61 °C) only the product of heterolytic reduction, 1-(4'-bromophenyl)ethanol, was formed. The reduction of 4-bromobenzophenone (**III**) at 23 °C gave a quantitative yield of 4-bromobenzhydrol but when the reduction was carried out at 61 °C, 0.6% of the debrominated reduction product, benzophenone, could be detected. The reduction of the more hindered halo ketones, halophenyl mesityl ketones (**IVa-c**), with LDPA appears to proceed by both homolytic (dehalogenation) and heterolytic pathways. When the reduction of THF solutions of 4-bromophenyl mesityl ketone, 4-BPMK (**IVa**), was either carried out at 23 °C or 61 °C the ratio polar/radical reduction was approximately 2/1. In the more polar solvent, CH_3CN, the homolytic reduction was favored 1.6-3 times (see Table III-2). Neither the yield, nor the ratio, of reduction products was affected by added initiator (AIBN) or inhibitor (DNB). The free radical nature of the dehalogenation process was substantiated by carrying out the LDPA reduction of 4-BPMK in a solvent mixture of CH_3CN/1-hexene. The trapping products 4-hexyl-2',4',6'-trimethylbenzophenone and its corresponding carbinol were obtained in the product mixture. In this solvent mixture a third product, the dimer of 2',4',6'-trimethylbenzoylphenyl radical was also detected, see Table III-2 and Fig. III-6 below.

Table III-2. Reduction of Halophenyl Mesityl Ketones (X-2',4',6'-Trimethylbenzophenones, **IVa-c**) with LDPA in THF or CH_3CN[a]

Ketone (X)	[LDPA]/ [Ketone]	Condition	Yield, %			
						Starting Material
4-Br (**IVa**)	4.2[b]	THF, 61 °C, 1 h	0.33 ± 0.08	29.0 ± 0.05	75.1 ± 0.1	0.33 ± 0.01
	4.2[b]	THF, 61 °C, 3% AIBN, 11 h	0.26 ± 0.02	29.1 ± 2.9	73.0 ± 1.9	1.0 ± 0.6
	4.2[b]	THF, 61 °C, 3% DNB, 11 h	0.29 ± 0.01	32.8 ± 4.2	70.7 ± 2.2	0.6 ± 0.1
	5.9[c,d]	THF, 23 °C, 29 h	10.0 ± 1.1	3.0 ± 0.3	28.3 ± 1.4	57.0 ± 2.5
	5.9[d]	THF, 61 °C, 3.5 h	0.8 ± 0.1	31.5 ± 2.4	62.2 ± 3.21	trace
	5.7[e]	CH_3CN, 23 °C, 28 h	25.2 ± 1.2	4.4 ± 0.3	3.3 ± 0.2	66.8 ± 3.4
[LDPA] = 0.101 M	8.3[e]	CH_3CN, 61 °C, 15 h	51.7 ± 0.3	31.8 ± 1.2	18.6 ± 0.1	1.2 ± 0.6
	5.7[f,g]	7.2:1 CH_3CN/1-Hexene, 61 °C, 24 h	25.7 ± 1.4	20.1 ± 0.8	28.7 ± 1.2	1.4 ± 0.1
[LDPA] = 0.099 M	4.2	CH_3CN, 61 °C, 15 h, DCPH 0.35M	0.0	65.3	36.1	0.0
		DCPH 0.7 M	0.0	60.8	37.3	0.0

Continued.....

Table III-2. Reduction of Halophenyl Mesityl Ketones (X-2',4',6'-Trimethylbenzophenones, **IVa-c**) with LDPA in THF or CH_3CN[a] (Continued).

Ketone (X)	[LDPA]/ [Ketone]	Condition	Yield, %			
						Starting Marterial
3-Br (**IVb**)	1.9[h]	THF, 23 °C, 14 h	1.1 ± 0.1	0.50 ± 0.31	28.8 ± 5.1	69.8 ± 0.8
	1.9[h]	THF, 61 °C, 14 h	1.7 ± 0.5	16.2 ± 0.4	81.8 ± 3.9	2.1 ± 0.5
	7.9[i]	CH_3CN, 61 °C, 15 h	39.7 ± 2.5	26.2 ± 2.2	31.7 ± 2.6	7.3 ± 2.2
2-Br(**IVc**)	2.4[j]	THF, 23 °C, 18 h	13.8	5.5	50.6	32.4
	2.4[j]	THF, 23 °C, 6 d	0.5	28.1	69.5	1.50
[LDPA] = 0.101 M	2.4[j]	THF, 61 °C, 10.5 h	0.6	28.3	68.7	1.74
	9.6	CH_3CN, 61 °C, 15 h	56.9 ± 1.7	35.7 ± 2.1	9.9 ± 1.0	3.2 ± 0.8

[a] All the reactions were run in duplicate in degassed H tubes. All the products were analyzed by GC on 10% SE-30 column and identified by GC/MS (high resolution) and GC/IR upon comparison with authentic samples. [b] [Ketone] = 0.065 M. [c] Very weak EPR signal was observed during the course of the reduction of **IVa** with LDPA or with $LiAlH_4$ in THF at 23°C. [d] [Ketone] = 0.024 M. [e] [Ketone] = 0.025 M, [LDPA] = 0.143 M. [f] Three other products were identified by GC/IR and GC/MS: a dimer of 2,4,6-trimethylbenzoylphenyl radical (2.1%), 4-hexylphenyl mesityl ketone (6.2%), and its corresponding carbinol (1.9%). See experimental. [g] [Ketone] = 0.029 M. [h] [Ketone] = 0.077 M. [i] [Ketone] = 0.0127. [j] [Ketone] = 0.061 M.

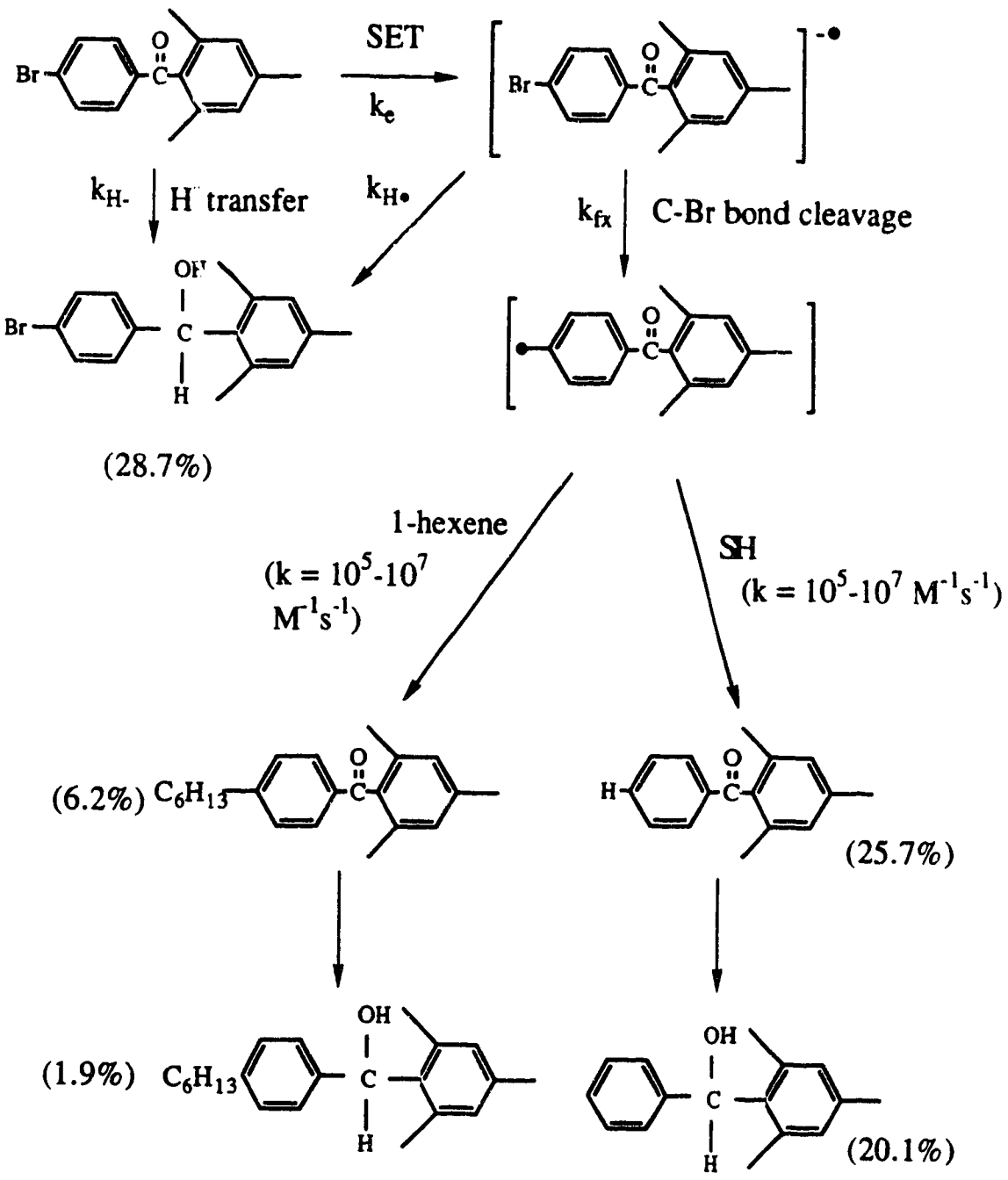


Fig. III-6. Trapping products 4-hexyl-2'4'6'-trimethylbenzophenone and its corresponding carbinol obtained from the LDPA reduction of **IVa** in the presence of 1-hexene.

With LDPA both mechanisms can conceivably lead to non-dehalogenated reduction products if hydrogen atom transfer is in competition with ketyl fragmentation. By changing the substitution pattern of the halogenated ketone, SM (**IVa-c**), the fragmentation rate constants for the halobenzophenone ketyls, $SM^{\bullet -}$, are affected and if there is a competition between fragmentation, k_{fX}, and abstraction, $k_{H\bullet}$, the ratio of nondehalogenated/dehalogenated, P_N/P_D, reduction products should reflect this change (*i.e.*, the haloketones with the smallest fragmentation rate constant should give the most halogenated alcohol). The relative ability to accept an electron would, presumably, not be much affected by the change in substitution pattern. Ketyl fragmentation rates, k_{fX}, for halogenated benzophenones have recently been reported.[11] The fragmentation rate constants are[14]: 2-bromo-:4-bromo-:3-bromobenzophenone; 10^5 sec^{-1}:10^5 sec^{-1}:10^3 sec^{-1}. A competitive formation of bromophenyl mesityl carbinol predicts an increase in the ratio, N/D, of 2-Br > 4-Br > 3-Br, however, since hydride transfer to 2-bromophenyl mesityl ketone (**IVc**) should be more sterically hindered than MPK itself, although the fragmentation rate is increased, the hydride transfer rate should be slowed down. The relative kinetics of formation of the products P_N/P_D can be derived from the expression given in Scheme III-2, eqs 17-20.

$$\text{LDPA} + \text{SM} \xrightarrow{k_{H^-}} \longrightarrow P_N \qquad (17)$$

$$\text{LDPA} + \text{SM} \xrightarrow{k_e} \longrightarrow SM^{-\bullet} \qquad (18)$$

$$\text{LDPA} + SM^{-\bullet} \xrightarrow{k_{H\bullet}} \longrightarrow P_N \qquad (19)$$

$$SM^{-\bullet} \xrightarrow{k_{fX}} \longrightarrow P_D \qquad (20)$$

Scheme III-2

Using a steady state treatment for the concentration of the ketyl, $[SM^{-\bullet}]$, two cases can be defined: Case 1, Halophenyl mesityl carbinol is formed by hydride transfer alone (*i.e.*, $k_{H\bullet} = 0$); Case 2, Halophenyl mesityl carbinol is formed by two pathways: hydride transfer (k_{H^-}) and electron transfer-hydrogen atom abstraction (k_e, $k_{H\bullet}$).

Case 1: where $k_{H\bullet} = 0$

$$\frac{P_N}{P_D} = \frac{k_{H^-}}{k_e}$$

Case 2:

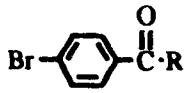
$$\frac{P_N}{P_D} = \frac{k_{H^-}}{k_e}\left[a + 1\right] + a$$

where: $a = \dfrac{k_{H\bullet}}{k_{fX}}$ [LDPA]

The ratio $k_{H\cdot}/k_e$ should be similar for the 2- and 4-substituted benzophenones since the difference in steric effects is negligible and the reduction potentials should be almost the same (E_o = -1.63 V, 4-bromobenzophenone; 3-bromobenzophenone, E_o = -1.57 V). The ketyl fragmentation rates (k_{fX}) however, are expected to differ by $>10^2$ sec^{-1}, and if $k_{H\cdot}$ and k_{fX} are competitive the mole fraction of alcohol formed from the reduction of 3-bromophenyl mesityl ketone (**IVb**) should be larger than the fraction formed from the reduction of the *para* isomer, **IVa**. The product ratio obtained for the reduction $P_N/(P_N+P_D)$ is consistent with the kinetics for reaction given for Case 2; see Table III-3 (CH_3CN, 61 °C, 15 h; 4-Br, $P_N/(P_N+P_D)$ = 0.18; 3-Br, $P_N/(P_N+P_D)$ = 0.30). The fraction, $P_N/(P_N+P_D)$ for the *ortho* isomer, 0.094, reflects not only the expected fast fragmentation rate $k_{f2\text{-}Br}$ $=>10^5$ sec^{-1} but also sterically hindered hydride transfer, if both processes are involved in the reduction.

When an efficient hydrogen atom donor, dicyclohexylphosphine (DCPH) was added the ketyl radical could be trapped, and if the alcohol found was the result of both hydride transfer and SET-hydrogen atom transfer then the fraction of nondehalogenated alcohol should increase. A comparison of the results of the reduction with added DCPH confirmed this competitive pathway since $P_N/(P_N+P_D)$ = 0.37 while the fraction without DCPH was 0.18 for the reduction of **IVa**, see Table III-2.

Table III-3. Deuterium Incorporation During the Reduction of the Aromatic Ketones.

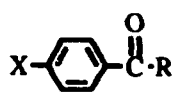
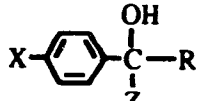
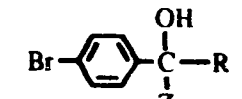


(R = CH_3, C_6H_5, Mesityl)

Substrate (R)	Condition	Products (%) X (%)	Z (%)	Yield (%)	SM (%)
CH_3 (II) [a]	THF-d8/LDPA	Br (100)	H (100)		30.2
	THF/LDPA-d24	Br (100)	D (100)	97.0	29.0
	CH_3CN/LDPA-d24 DCPH (0.35 M)	Br (100)	D (100)	94.7	4.1
Phenyl (III) [b]	THF-d8/LDPA	X(%) Br (100)	Z (%) H (100)		0.0
	THF/LDPA-d24	Br (100)	D (100)	98.3	0.0 [c]
	CH_3CN/LDPA-d24 DCPH (0.35 M)	Br(100)	D (100)	97.6	0.0 [d]

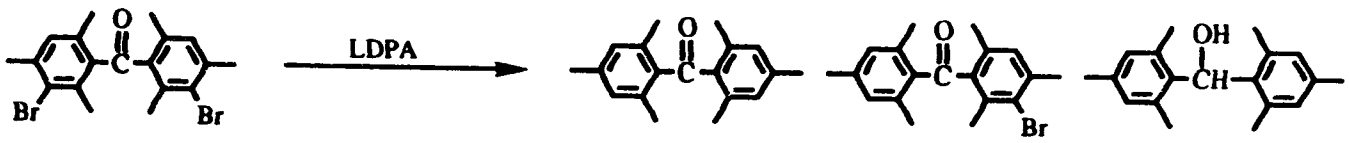
Continued.....

Table III-3. Deuterium Incorporation During the Reduction of the Aromatic Ketones (Continued).

Substrate (R)	Condition	Products (%)						
								
Mesityl (IVa)		X (%)	Yield (%)	X (%)	Z (%)	Yield (%)	Z (%)	Yield (%)
	THF/ LDPA-d24 [e]	D (28)	6.4	D (28)	D (100)	14.2	D (100)	83.1
		H (72)		H (72)				
	THF-d8/ LDPA [f]	D (6)	0.67	D (6)	H (100)	27.3	H (100)	76.4
		H (94)		H (94)				
	CH3CN/ LDPA-d24 DCPH (0.35 M) [g]			D (18)	D (68)	65.3	D (68)	36.1
				H (82)	H (32)		H (32)	

[a, b] [Ketone] 0.010 M, [LDPA] = 0.047 M, 61 °C, 24 h. [c] 0.8% of PhCDOH was detected. [d] 0.76% of PhCDOH was detected. [e] [IVa] = 0.067 M, [LDPA] = 0.177 M, 23 °C, 48 h. [f] [IVa] = 0.067 M, [LDPA] = 0.35 M, 23 °C, 48 h. [g] [IVa] = 0.024 M, [LDPA] = 0.099 M, 61 °C, 15 h.

Table III-4. The Reduction of 3,3'-Dibromo-2,2',4,4',6,6'-hexamethylbenzophenone (V) with LDPA.



Conditions[a]		Products %		S.M. (%)
THF, 23 °C, 24 h	5.9 ± 1.6	24.4 ± 0.8	0.0	68.0 ± 2.3
THF, 61 °C, 22 h	98.9 ± 1.2	0.0	3.3 ± 0.3	0.0

[a] [V] =0.00462 M, [LDPA] = 0.050 M.

The reduction of 4'-bromoacetophenone (**II**) appears to proceed primarily via the hydride transfer pathway, since during the reduction of **II** no dehalogenation was detected while the analysis of the reduction products of **III** showed only traces of benzhydrol. The reduction of **II**, **III**, and **IVa** in acetonitrile with LDPA-d_{24} yielded 100% α-D carbinol, see Table III-3. Since no dehalogenation was observed from the reactions of **II** and only a small amount of dehalogenated product was formed from the reduction of **III**, halogenated carbinol formation could possibly have come from the reaction of the ketyl prior to fragmentation. Carbinols, both halogenated and dehalogenated, are formed during the reduction of **IVa**. For this substrate, **IVa**, direct evidence for the formation of a ketyl as a major intermediate is obtained (dehalogenation), however, halogenated carbinol formation can also be due to ketyl radical hydrogen atom-abstraction as well as hydride transfer. The source of hydrogen from either homolytic or heterolytic reduction remains to be established. When the reductions are carried out in THF-d_8 with LDPA or in THF or acetonitrile with LDPA-d_{24} it is clear that during dehalogenation of **IVa** the phenyl radical abstracts H or D from LDPA or from solvent, while the source of the carbinol-α-H or D is entirely from LDPA, or LDPA-d_{24}.

In order to elucidate the mechanism responsible for carbonyl reduction, *i.e.*, homolytic or heterolytic hydrogen transfer from LDPA, the reduction of the three halogenated probes (**II**, **III**, **IVa**) was carried out with LAPA-d_{24} in the presence of added DCPH. The reduction of **IVa** with LDPA-d_{24} with added DCPH confirmed that the ketone transformation to carbinol proceeded to a large extent by hydrogen atom abstraction via the ketyl radical ion since the intermediate, ketyl radical

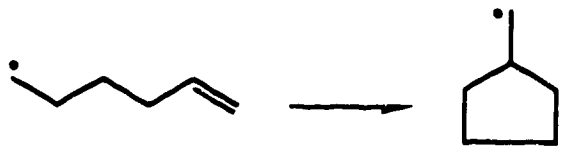
anion, was trapped by the hydrogen donor, DCPH, see Table III-3. However, the reductions of either 4-bromobenzophenone or 4'-bromoacetophenone with LDPA-d_{24} in the presence of added DCPH did not show hydrogen incorporation at the α-carbon of carbinol from DCPH the reductions of either 4-bromobenzophenone or 4'-bromoacetophenone most probably proceeds by hydride transfer, see Table III-3. The reduction of the most hindered ketone, 3,3'-dibromo-2,2',4,4',6,6'-hexamethylbenzophenone (**V**), with LDPA gave only homolytic products, see Table III-4. The hydride transfer was totally blocked by the sterically hindered LDPA and the hindered ketone probe, **V**, while the electron transfer still proceeds.

The Rearrangement Probe - Since 6-halo-1-hexene had been reported to yield methylcyclopentane during its reduction with LDPA[9] and since LAH gives cyclized product[15] with 2,2-dimethyl-1-halohexene (x = Br, I) the purified LDPA was allowed to react with 6-halo-1-hexene. The products of this reduction are listed in Table III-5.

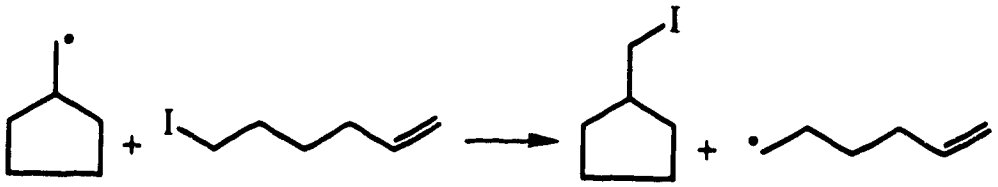
Only minor amounts methylcyclopentane (4-9%) diagnostic of radical cyclization are formed during the reaction of 6-iodo-1-hexene (**VIa**), while no cyclized products are formed during the reaction of 6-bromo-1-hexene (**VIb**). Only when the reaction is carried out in the presence of a small amount of a radical initiator, AIBN (3%), are traces (0.6%) of the cyclized product produced during the reaction of 6-bromo-1-hexene (**VIb**). The structure of the 3-alkylated pyridine from both substrates had only the uncyclized sidechain.

An alternative mechanism for the reductive cyclization of 6-iodo-1-hexene has been suggested.[12h] In this sequence of reactions the radical

cyclization product, 1-methylcyclopentane, can be formed by a chain reaction which does not involve the reagent as a chain carrier in the cyclization, Scheme III-3.



(21)



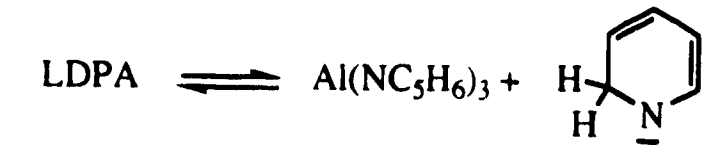
(22)

Scheme III-3

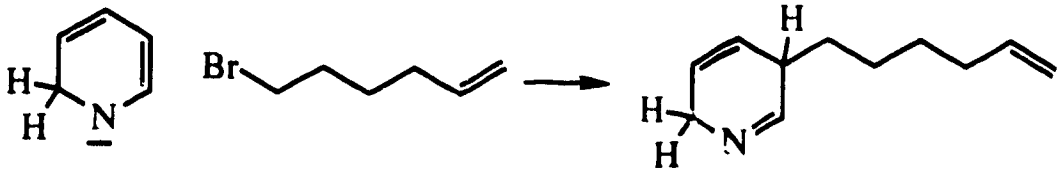
Since reduction takes place after the formation of the cyclized iodide the substrate loses its usefulness as a radical cyclization probe. The minor (4-9%) amount of cyclized hydrocarbon formed in the LDPA reduction, Table III-5, does not unequivocally confirm the involvement of a radical process. A more unequivocal probe is the use of 6-bromo-1-hexene as a cyclization probe. The halogen transfer step for 6-bromo-1-hexene does not take place rapidly enough to carry the chain.[12h] A further advantage afforded by the use of the bromohexene is that the S_N2 substitution by pyridine and by the pyridyl anion is slower than the substitution of the alkyl iodide.

As expected no cyclization was detected when the bromide was reduced by LDPA and no N-substituted pyridinium salt was formed. However, due to the strongly nucleophilic pyridyl anion, an almost quantitative yield of the 3-substituted pyridine was formed (eqs 23-25).

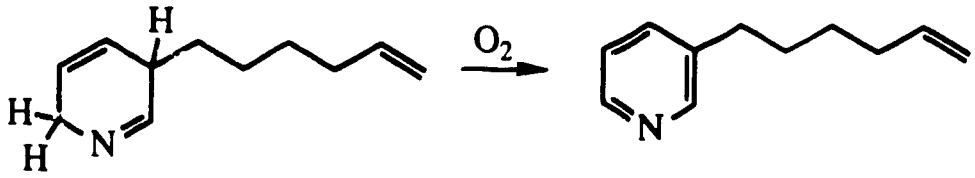
Only with 3% of added AIBN was a small amount (<1%) of cyclized material detected.



(23)

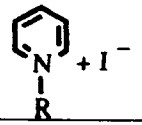


(24)



(25)

Table III-5. The Reaction of 6-Halo-1-hexene (**VIa-b**) with LDPA (THF).[a]

Substrate	Conditions	Products (%)[b,c]			S.M. (%)
					
6-iodo-1-hexane	23 °C, 20 h[d]	45.0	8.5	10.5	33.5
	23 °C, 20 h[e]	16.0	4.4	35.7	41.8
	61 °C, 20 h	57.6	9.4	26.4	8.2
6-bromo-1-hexane	61 °C, 36 h	95.9	0	0	4.2
	61 °C, 36 h, 3% AIBN	94.9	0.6	0	4.5

[a] [LDPA]/[RX] = 1.77; [RX] = 0.122 M. [b] R = 5-hexenyl. [c] In all the reactions, 3-5% of dihexenylpyridine was detected (GC/MS). [d] [LDPA]/[RX] = 1.77; [RX] = 0.083 M. [e] Non-degassed.

Conclusions

A series of chemical probes was employed in a systematic study on polar vs SET reactions of LDPA. Ketyl radicals were observed in the LDPA reduction of hindered aromatic ketones, MPK and DMK. A SET process, which is competitive with a polar process in the LDPA reduction, is substantiated by the fact that dehalogenated reduction products were produced when bromophenyl ketones were used as probes in the investigation. The intermediate 4-(2',4',6'-trimethylbenzoyl)phenyl radical was trapped by 1-hexene to give 4-hexyl-2',4',6'-trimethylbenzophenone. The ketyl radicals from 4-bromo-2',4',6'-trimethylbenzophenones were also trapped by a good hydrogen donor, DCPH, to give halogenated alcohols. Deuterium labelling experiments indicate that the ketyl radicals cannot abstract hydrogen or deuterium atoms from the solvent THF or THF-d_8. When the even more hindered ketone probe, 3,3'-dibromo-2,2',4,4',6,6'-hexamethylbenzophenone, was used the SET process was shown to be the only reaction pathway, since only dehalogenated products were observed. SET-radical processes were also observed in the reactions of LDPA with strong electron acceptors, 2,6-di-*t*-butylbenzoquinone and bromotriphenylmethane, and with the cyclizable probe, 6-bromo-1-hexene.

It is suggested that the reactions of LDPA with organic substrates proceed by both homolytic and heterolytic pathways. The heterolytic process is the dominant reaction. When the substrate is sterically hindered a homolytic reduction mechanism is preferred. When the substrate used is a very good electron acceptor homolytic processes predominate.

Experimental

General -The solutions of all oxygen- and water-sensitive hydride reagents were prepared in a drybox under a N_2 atmosphere. The transfer of the solutions was performed with gas tight syringes using standard techniques. All the reduction reactions were carried out in flame dried H tubes which were degassed before they were sealed.

Instrumentation -^1H and ^2H NMR spectra were obtained using either a Bruker AM-400 (400 MHz) or Bruker WH-200 (200 MHz) NMR spectrometer with deuteriochloroform as solvent and residual chloroform (δ 7.24) as an internal lock. EPR spectra were obtained using a Bruker ER200E/SRC spectrometer fitted with a ER4102 ST-Universal X-Band Resonator operated at 9.6 GHz. Coupling constants are reported in gauss, and the g values were determined using a diphenylpicryhydrazyl (DPPH) external standard. IR spectra were recorded on a Perkin-Elmer Model 1600 FT/IR spectrometer. High-resolution mass spectral data were obtained with a KRATOS MS50 high-resolution EI^+ mass spectrometer (70 ev) connected to a DS 55 data system. The isotopic content of the products was conveniently determined by GC/MS in conjunction with ^1H and ^2H NMR. In order to avoid possible error due to partial separation of the isotopic mixtures by GC, the mass fragmentography technique was employed. Thus, the total ion mass of each compound (m/z) was integrated for each GC peak and used as the numerical value for the analytical calculations. When an isotopic composition was obtained based on a

fragment ion, it can be assumed that the fragmentation occurred without any isotope effect. Gas phase chromatograph/mass spectra (GC/MS) were recorded using a VG-70E mass spectrometer interfaced to a Varian Vista 6000 GC fitted with a DB-1 capillary column interfaced to a 11-250 data system. Gas phase chromatograph/infrared spectra (GC/IR) were obtained using a HP-5965A IRD spectrometer interfaced to a HP5890 gas chromatograph (Hewlett-Packard) fitted with a glass capillary column (Hewlett-Packard ultra 2, 25 m x 0.32 mm x 0.52 μ).

Materials -Tetrahydrofuran (Aldrich, HPLC grade) was dried over KOH and distilled from sodium benzophenone ketyl immediately prior to use. **THF-d8** (GIC, 99% D) was purified by the same method. **Acetonitrile** (Aldrich, reagent grade) was purified by the standard procedure[15] and distilled from CaH_2 before use. **N,N-dimethylformamide** (DMF, Aldrich, 99%, A.C.S. spectrophotometric grade) was distilled from CaH_2 prior to use.

Lithium aluminum hydride (General Intermediates of Canada) was dissolved in diethyl ether, filtered and recovered after the ether was evaporated. **Lithium aluminum deuteride** (Aldrich, 98% atom D) was used as supplied.

LDPA, I, and LDPA-d_{24} (prepared from $LiAlD_4$ and Py-d_5) were prepared at 23 °C.[4,16]

Bromotriphenylmethane (Aldrich, 98%) was recrystallized from benzene/pet. ether (35-60 °C)[17] mp 153-154.5 °C (lit.[17] mp 152-154 °C): Anal. Calcd for $C_{19}H_{15}Br$: C, 70.60; H, 4.68. Found: C, 70.83; H, 4.70.

α,α'-Azobis(isobutyronitrile) (Aldrich) was recrystallized from ethanol-water, mp 102 °C (lit.[18] mp 103 °C). ***m*-Dinitrobenzene** (Fisher) was recrystallized from methanol, mp 91.5-92 °C (lit.[18] mp 88-90 °C). **1,4-Di-*t*-butylbenzene** (Aldrich), the internal GC standard, was recrystallized from ethanol and dried in vacuum over P_2O_5 at 55 °C, mp 78-79 °C (lit.[18] mp 80 °C).

2,6-Di-*t*-butylbenzoquinone (Aldrich, >98% purity, mp 65-67 °C) and **dicyclohexylphosphine** (Aldrich) were used as received.

Benzophenone (Fisher) was recrystallized from pet. ether (35-60 °C)/acetone, mp 49-50.5 °C (lit.[18] mp 49-51 °C).

Dimesityl ketone (Aldrich) was recrystallized from pet. ether (35-60 °C)/acetone, mp 139-140.5 °C (lit.[18] mp 138-140 °C).

4'-Bromoacetophenone (II) (Aldrich) was recrystallized from ethanol/water, mp 51-52 °C (lit.[18,19] mp 50-52 °C).

4-Bromobenzophenone (III) (Aldrich) was recrystallized from ethanol/pet. ether (35-60 °C), mp 80.5-81.5 °C (lit.[18,19] mp 80-82.5 °C), Anal. Calcd for $C_{13}H_9OBr$: C, 59.80; H, 3.47. Found: C, 59.60; H, 3.39.

Mesityl phenyl ketone (2,4,6-trimethylbenzophenone), bromophenyl mesityl ketones (2-, 3-, or 4-bromo-2',4',6'-trimethylbenzophenone, IVa-c) and 4-hexyl-2',4',6'-trimethylbenzophenone were prepared by treating a CS_2 solution of corresponding bromobenzoyl chlorides with mesitylene in the presence of aluminum trichloride.[20] The products were isolated and purified by recrystallization from pet. ether (35-60 °C)/acetone.

Mesityl phenyl ketone: mp 34-35 °C (lit.[20] mp 34-35.5 °C); bp 161-163 °C/4.5 mmHg (lit.[27] bp 180-182 °C/8.5 mm Hg); ^1H NMR (200

MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.60 (m, 1H), 7.46 (m, 2H), 6.94 (s, 2H), 2.37 (s, 3H), 2.08 (s, 6H); HRMS, *m/z*+, 224.1201 (Calcd for $C_{16}H_{16}O$: 224.1201); IR (Gas phase) ν 3072, 2932, 1815, 1887, 1609, 1450, 1387, 1284, 1173, 1026, 910, and 849 cm^{-1}.

4-Bromophenyl mesityl ketone, IVa: mp 71.5-72.5 °C (lit.[20] mp 70-72 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 7.62 (AA'BB', 4H), 6.92 (d, 2H), 2.34 (s, 3H), 2.06 (s, 6H); HRMS, *m/z*+ 304.0284, 302.0307 (Calcd for $C_{16}H_{15}O^{81}Br$: 304.0289; $C_{16}H_{15}O^{79}Br$: 302.0306); IR (Gas phase) ν 3019, 2933, 1688, 1587, 1481, 1396, 1263, 1171, 1071, 1013, 907, and 847 cm^{-1}; Anal. Calcd for $C_{16}H_{15}OBr$: C, 63.33; H, 5.05; Br, 26.35. Found: C, 63.38; H, 4.99; Br, 26.35.

3-Bromophenyl mesityl ketone, IVb: mp 88-89 °C (lit.[21] mp 87-89 °C); ^1H NMR (200 MHz, CD_2Cl_2) δ 7.94 (m, 1H), 7.70 (t-m, 2H), 7.34 (t, 1H), 6.94 (s, 2H), 2.35 (s, 3H), 2.06 (s, 6H); HRMS, *m/z*+, 304.0282, 302.0300 (Calcd for $C_{16}H_{15}O^{81}Br$: 304.0289; $C_{16}H_{15}O^{79}Br$: 302.0306); Anal. Calcd for $C_{16}H_{15}OBr$: C, 63.33; H, 5.05; Br, 26.35. Found: C, 63.61; H, 5.10; Br, 26.44.

2-Bromophenyl mesityl ketone, IVc: mp 113-114 °C (lit.[27] 113-4 °C); ^1H NMR (400 MHz, CD_2Cl_2) δ 7.70 (m, 1H), 7.40-7.30 (m, 3H), 6.90 (s, 2H), 2.33 (s, 3H), 2.12 (s, 9H); HRMS, *m/z*+, 304.0286, 302.0304 (Calcd for $C_{16}H_{15}O^{81}Br$: 304.0289; $C_{16}H_{15}O^{79}Br$: 302.0306); Anal. Calcd for $C_{16}H_{15}OBr$: C, 63.33; H, 5.05; Br, 26.35. Found: C, 63.28; H, 4.92; Br, 26.59.

3,3'-Dibromo-2,2',4,4',6,6'-hexamethylbenzophenone (V) was prepared by treating a mixture of dimesitylketone (3.2 g, 12 mmol), 20 mL CCl_4, 0.05 g $FeCl_3$ and a piece of I_2 with a solution of 1.5 mL

bromine (28 mmol) in 10 mL CCl_4. The bromine solution was added dropwise while the mixture was stirred at r t . After 1 h, the mixture was heated at reflux for 4 h. The mixture was diluted with ether, washed with aqueous 10% $NaHCO_3$ solution, 5% sodium thiosulfate, and water. The solvent was evaporated and white solid was obtained. After flash chromatography (silica gel, 20-45 microns, pH 7.1) using 5:95 diethyl ether/hexane as eluant, recrystallization from ether/hexane yielded 2.7 g, 52%, of a white solid: mp 103-104 °C. GC (on SE-30) showed one peak. TLC (silica gel, 5/95 Diethyl ether/hexane) showed one spot. ^1H NMR (200 MHz, $CDCl_3$) δ 6.90 (s, 2H), 2.36 (s, 6H), 2.25 (s, 6H), 2.00 (s, 6H). Anal. Calcd for $C_{19}H_{20}Br_2O$: C, 53.80; H, 4.75. Found: C, 53.73; H, 4.86. HRMS, *m/z*+ 425.9840 (Calcd for $C_{19}H_{20}{}^{81}Br_2O$: 425.9840).

6-Bromo-1-hexene (VIb) (Aldrich) was purified by vacuum distillation, bp 68-69 °C/31 mm Hg (lit.[18] bp 47-51 °C/16 mm Hg).

6-Iodo-1-hexene (VIa) was prepared by treating 6-bromo-1-hexene (Aldrich) with NaI in dry acetone under a nitrogen atmosphere. Fractional distillation gave a colorless liquid: bp 48-49 °C/1.0 mm Hg or 86-88 °C/40 mm Hg (lit.[12b,9] bp 64-66 °C/12 mm Hg); ^1H NMR ($CDCl_3$, 200 MHz) δ 5.89-5.69 (m, 1H), 5.07-4.93 (m, 2H), 3.22-3.15 (t, 2H), 2.14-2.02 (m, 2H), 1.91-1.77 (m, 2H), 1.57-1.42 (m, 2H); HRMS, *m/z*+ obsd 209.9908 (M^+, Calcd for $C_6H_{11}I$ 209.9906); IR (Gas phase) ν 3088, 2999, 2864, 1836, 1643, 1445, 1352, 1288, 1221, 993, and 918 cm^{-1}. Anal. Calcd for $C_6H_{11}I$: C, 34.31; H, 5.28. Found: C, 34.02; H, 5.05.

Dimesitylcarbinol was prepared from the reaction of mesitaldehyde and mesitylmagnesium bromide,[22] mp 150-150.5 °C (lit.[22] 149.5-150 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 7.10 (s, 4H), 6.65 (s, 1H),

2.57 (s, 6H), 2.52 (s, 12H); Anal. Calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01. Found: C, 85.21; H, 9.07.

Dimesitylmethane was prepared by Baeyer's method,[23] mp 134-135 °C (lit.[23] 130-135 °C); Anal. Calcd for $C_{19}H_{24}$: C, 90.42; H, 9.58. Found: C, 90.28; H, 9.44.

2,4,6-Trimethylbenzhydrol and bromo-2',4',6-trimethylbenzhydrol were prepared by the $NaBH_4$ reduction of the corresponding ketones (**IVa-c**) in 98% ethanol, then recrystallized from diethyl ether/hexane.

2,4,6-Trimethylbenzhydrol: bp 142-144 °C/0.2 mm Hg (lit.[26] 154.5-157 °C/0.3 mm Hg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 5H), 6.88 (s, 2H), 6.30 (s, 1H), 2.28 (s, 3H), 2.20 (s, 6H). HRMS, *m/z*+ obsd 226.1358 (Calcd for $C_{16}H_{18}O$: 226.1358); IR (Gas phase) ν 3650, 3027, 2934, 2876, 1945, 1885, 1804, 1724, 1609, 1460, 1453, 1352, 1173, 1014, and 846 cm^{-1}; Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.79; H, 7.93.

4-Bromo-2',4',6'-trimethylbenzhydrol: bp 165-167 °C/0.01 mm Hg; ^1H NMR (200 MHz, $CDCl_3$) δ 7.42 (AA', 2H) 7.12 (BB', 2H), 6.85 (s, 2H), 6.25 (s, 1H), 2.28 (s, 3H), 2.23 (s, 6H). HRMS, *m/z*+ obsd 306.0438, 304.0463 (Calcd for $C_{16}H_{17}OBr$: 306.0442, 304.0462); IR (Gas phase) ν 3651, 2935, 1611, 1488, 1398, 1170, 1073, 1012, and 848 cm^{-1}; Anal. Calcd for $C_{16}H_{17}OBr$: C, 62.96; H, 5.61. Found: C, 63.12; H, 5.67.

2-Bromo-2',4',6'-trimethylbenzhydrol: mp 109-110 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46 (d, 1H), 7.35 (d, 1H), 7.17 (t, 1H), 7.06 (t, 1H), 6.75 (s, 2H), 6.17 (s, 1H), 2.17-2.12 (d, 9H). HRMS, *m/z*+ obsd

306.0440, 304.0466 (Calcd for $C_{16}H_{17}O^{81}Br$, $C_{16}H_{17}O^{79}Br$; 306.0442, 304.0462); IR (Gas phase) ν 3629, 3070, 3016, 2936, 2879, 1921, 1812, 1725, 1610, 1570, 1445, 1386, 1300, 1189, and 1133 cm^{-1}; Anal. Calcd for $C_{16}H_{17}OBr$: C, 62.96; H, 5.61. Found: C, 62.91; H, 5.58.

3-Bromo-2',4',6'-trimethylbenzhydrol: bp 178-179 °C/0.02 mm Hg; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25 (m, 4H), 6.85 (s, 2H), 6.32 (s, 1H), 2.42 (s, 3H), 2.25 (s, 6H); HRMS, *m/z*+ obsd 306.0439, 304.0465 (Calcd for $C_{16}H_{17}O^{79}Br$, $C_{16}H_{17}O^{81}Br$; 306.0442, 304.0462); Anal, Calcd for $C_{16}H_{17}OBr$: C, 62.96; H, 5.61. Found: C, 62.87; H, 5.57.

4-Hexyl-2',4',6'-trimethylbenzophenone: bp 153-155 °C/0.02 mm Hg (lit.[27] bp 205-210 °C/4 mm Hg); ^1H NMR (200 MHz, $CDCl_3$) δ 7.75 (d, 2H), 7.30 (d, 2H), 6.95 (s, 2H), 2.74 (t, 2H), 2.40 (m, 5H), 2.12 (s, 6H), 1.75-0.85 (m, 11H). HRMS, *m/z*+ obsd 308.2141 (Calcd for $C_{22}H_{28}O$: 308.2140); IR (Gas phase) ν 2936, 1869, 1683, 1606, 1445, 1387, 1264, 1171, 1018, 909, and 848 cm^{-1}; Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15. Found: C, 85.39; H, 9.06.

4-Hexyl-2',4',6'-trimethylbenzhydrol: bp 176-178 °C/0.05 mm Hg (lit.[27] bp 205-210 °C/4 mm Hg); ^1H NMR (200 MHz, $CDCl_3$) δ 8.71 (bd, OH), 7.18 (AA', 4H), 6.88 (s, 2H), 6.32 (s, 1H), 2.64 (t, 2H), 2.32 (s, 3H), 2.28 (s, 6H), 7.00-0.95 (11H). HRMS, *m/z*+ obsd 310.2299 (Calcd for $C_{22}H_{30}O$: 310.2297); IR (Gas phase) ν 3650, 3021, 2935, 2871, 1721, 1610, 1010, 1509, 1351, 1170, 1015, and 848 cm^{-1}; Anal. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74. Found: C, 85.34; H, 9.65.

4,4'-Di-(2,4,6-trimethylbenzoyl)-biphenyl[*p*-Dimer of 2',4',6'-trimethylbenzophenone]: HRMS, *m/z*+ obsd 446.2241 (Calcd

for $C_{32}H_{32}O_2$: 446.2246); IR (Gas phase) ν 3100-2900, 1685, 1607, 1423, 1281, 1173, 1000, 909, and 850 cm^{-1}.

3-(6-Hexenyl)-pyridine: bp 88-90 °C/5 mm Hg (lit.[28] bp 75-77 °C/2 mm Hg); ^1H NMR (200 MHz, $CDCl_3$) δ 8.42 (m, 2H), 7.48 (m, 1H), 7.22 (m, 1H), 5.79 (m, 1H), 4.98 (m, 2H), 2.61 (t, 2H), 2.08 (m, 2H), 1.72-1.26 (m, A_2B_2 type, 4H); HRMS, *m/z*+ obsd 161.1204 (M^+, Calcd for $C_{11}H_{15}N$ 161.1205); IR (Gas phase) ν 3034, 2937, 2867, 1643, 1575, 1424, 1351, 1189, 1125, 993, and 915 cm^{-1}; Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38. Found: C, 82.12; H, 9.45.

General procedure for the reduction of substrates with LDPA and the quantitative GC analysis of the products - An aliquot of a solution of LDPA (0.05-0.25 M) in the desired solvent (THF, CH_3CN) was placed in one arm of a Pyrex H tube, an aliquot of a solution of the substrate (0.02-0.025 M) in the same solvent containing 1,4-di-*t*-butylbenzene (with or without the additive AIBN, *m*-DNB or DCPH) was placed in the other arm of the H tube. The tube was degassed under vacuum (three times) and sealed. The two solutions were thermostated at the desired temperature and mixed. The reaction was carried out for the time specified, see Tables III-1-5. The reaction tube was cooled, opened, quenched with dilute HCl, and dried with anhydrous $MgSO_4$. The reaction mixtures were analyzed by GC.

The product mixture from the reduction of 4'-bromoacetophenone (**II**) and 4-bromobenzophenone (**III**) were analyzed using a 25 ft x 1/4 inch stainless steel column packed with 10% FFAP on Chromosorb, WAW DMCS, 60/80 mesh. The product mixtures from the reductions of bromophenyl mesityl ketones (**IVa-c**), 3,3'-dibromo-2,2',4,4',6,6'-

hexamethylbenzophenone (V), 6-halo-1-hexenes (**VIa-b**), and bromotriphenylmethane were analyzed using a 25 ft x 1/4 inch stainless steel column packed with 10% SE-30 on Chromosorb, WAW DMCS, 60/80 mesh. GC analysis was carried out using a HP5840A gas chromotograph equipped with a hydrogen flame detector interfaced to a HP5840A integrator. The area ratios were converted to mole ratios for quantitative determinations by using standard calibration curves constructed from known mixtures of the authentic materials. Products were identified by a comparison of their retention times, GC/MS, GC/IR spectra, with those of authentic materials. The quantitative results listed in Tables III-1-5 are the average results of two or more independent experiments.

Competitive reductions - An aliquot of a solution of the two ketones in THF containing GC internal standard and an aliquot of a solution of LDPA in degassed H tubes were thermostated at the desired temperature, mixed, and allowed to react for a desired period of time. The reaction mixtures were quenched and analyzed as above.

Isotope-labelling study - The reductions of substrates (**II-IVa**) with LDPA-d_{24} in THF or CH_3CN or with LDPA in THF-d_8 were carried out as above. The purified products were analyzed by GC, ^1H NMR, ^2H NMR, and mass spectroscopy to determine the deuterium content of a particular product.

EPR spectroscopy of the reaction mixtures from LDPA or LAH and the substrates: bromotriphenylmethane, 2,6-di-*t*-butylbenzoquinone, dimesitylketone, mesityl phenyl ketone, and benzophenone - A THF solution of the substrate (0.02 M) was placed in one of the divided arms of a H tube fitted also with a quartz EPR tube. A

second THF solution of LDPA (2.0 mL, 0.02 M) was placed in the second arm of the H tube and the reaction vessel was degassed three times, and then sealed. The solutions were mixed at room temperature and the filled EPR tube was immediately placed into the cavity of the EPR spectrometer and the spectra were recorded.

Triphenylmethyl radical[24] and 2,6-di-*t*-butylbenzoquinone ketyl[10c] radical were observed in a few minutes after the solution of LDPA and the solution of the corresponding substrate were mixed. Their spectra are identical to those reported in the literature.[24,10c]

The mesityl phenyl ketyl radical was obtained after the solution of mesityl phenyl ketone and the solution of LDPA were mixed for an extended period of time (2 d). The EPR spectrum is identical to that appearing in the literature.[9] The same spectrum was obtained when a THF solution of MPK and a THF solution of $LiAlH_4$ were mixed (several min).

The dimesityl ketyl radical was observed after the solutions were mixed and allowed to react for an extended period of time (5 d). The spectrum is identical to that in the literature.[9] The same EPR spectrum was obtained when a THF solution of DMK and a THF solution of $LiAlH_4$ were mixed (2 min). After 24 h, the spectrum assigned to the dimesityl methinyl radical was observed. The EPR spectrum is identical to that appearing in the literature.[13]

No EPR signal was obtained from the reaction of benzophenone with LDPA.

No reaction was observed between dimesityl carbinol and LDPA. No reaction was observed either between dimesitylmethane and LDPA or between dimesitylmethane and $LiAlH_4$.[25]

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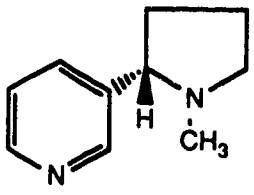
CHAPTER 4

An Application of Dihydropyridines in the Synthesis of Natural Products: A Simple Synthesis of (±)-1,2,3,6-Tetrahydro-2,3'-bipyridine (Anatabine) and (±)-3-(2-Piperidinyl)pyridine (Anabasine).[1]

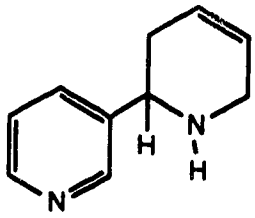
Introduction

Anatabine (I) is the most abundant of the minor alkaloids of the tobacco plants.[2] In fresh *Nicotiana tabacum L.*, the plant from which it was first isolated,[3] the alkaloid mixture consists of 93% nicotine, 3.9% anatabine, 2.4% nornicotine, 0.5% anabasine (II), and a small amount of other alkaloids.[2]

Tobacco Alkaloids:

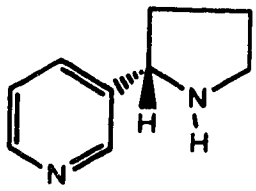


Nicotine

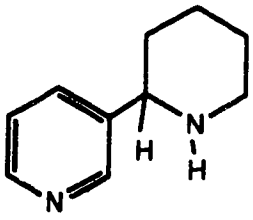


I, Anatabine

(S)- or (±)-

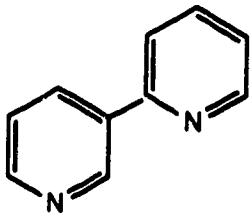


Nornicotine

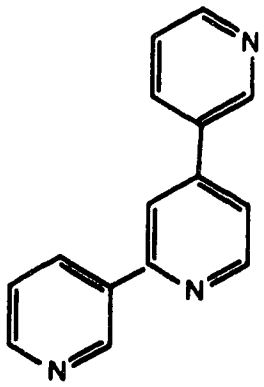


II, Anabasine

(S)- or (±)-

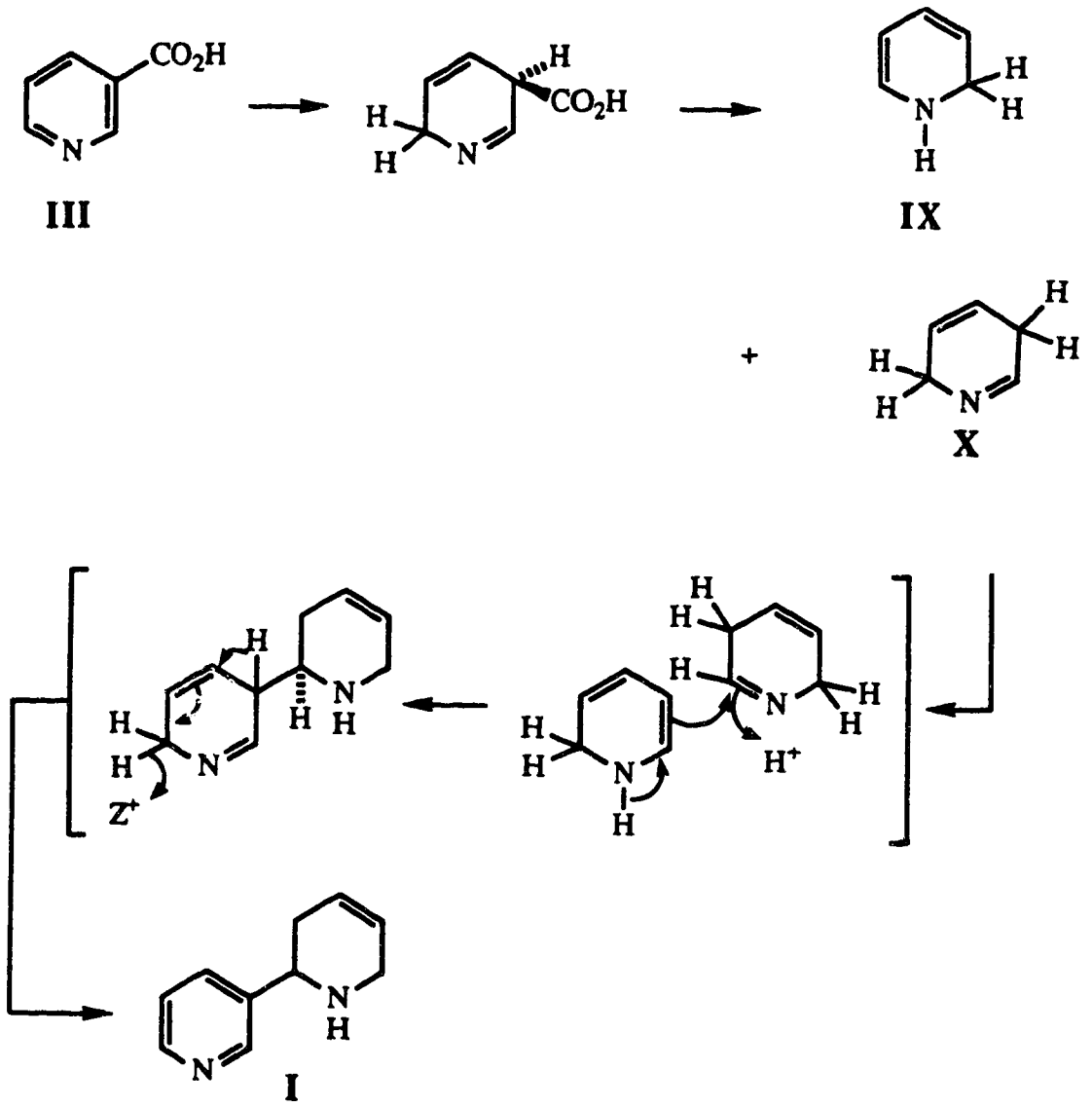


α,β-Bipyridyl



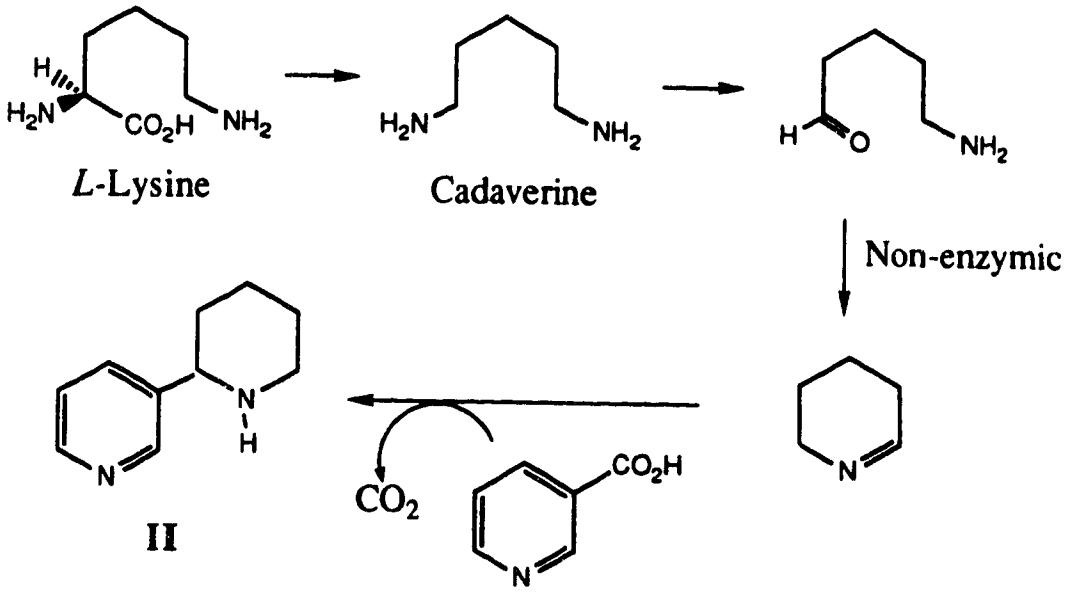
Nicotelline

Short term $^{14}CO_2$ feeding experiments indicate that anabasine is not a precursor to anatabine.[4] Although, in both anabasine and anatabine the genesis of the pyridine ring is nicotinic acid, **III**,[2,5a] the source of the piperidine and dehydropiperidine rings are from different biological precursors.[5b-8] It is well established that the piperideine ring of anatabine is also derived from nicotinic acid, but the piperidine ring of anabasine is derived from lysine (see Scheme IV-1 and Scheme IV-2).



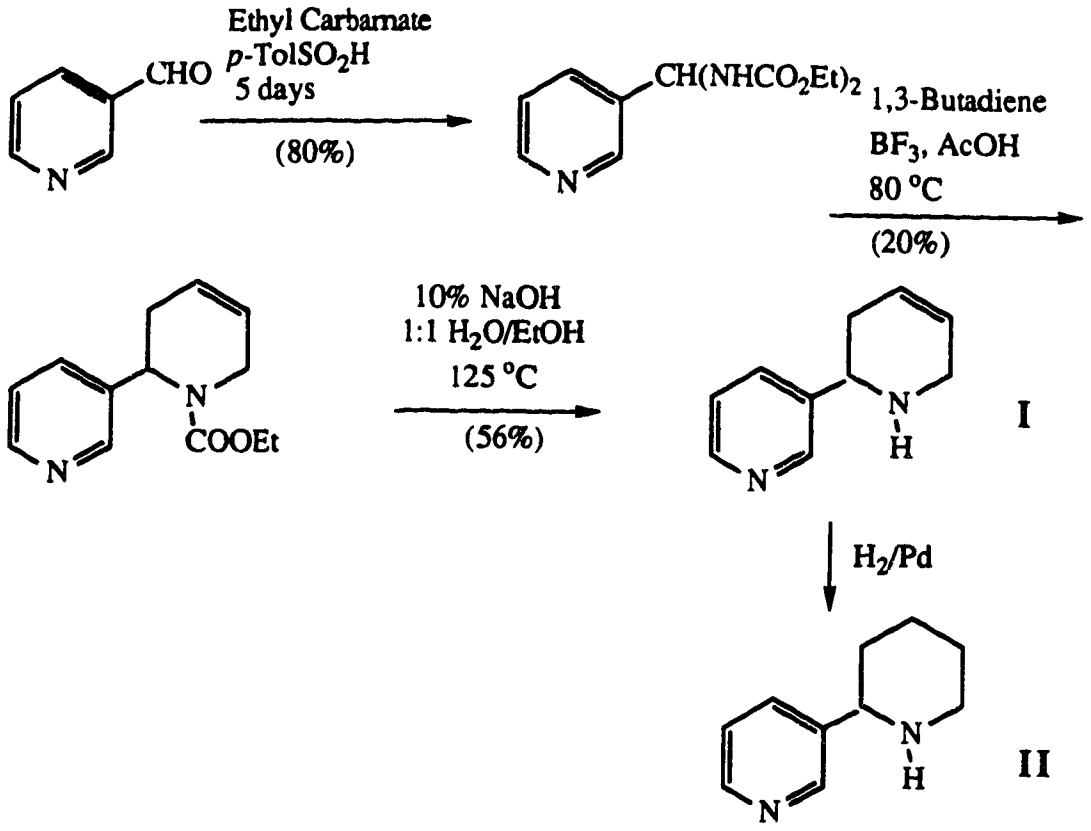
Scheme IV-1

Biosynthesis of Anabasine:

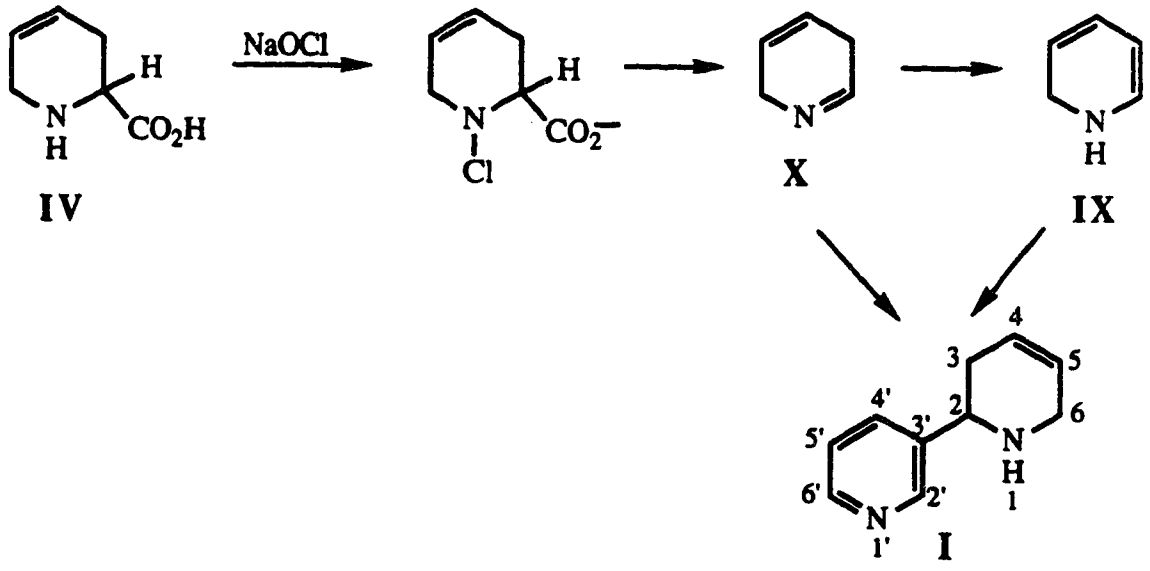


Scheme IV-2

The total synthesis of anatabine has been reported by three groups of workers.[7b,9,10] The first synthesis from 3-formylpyridine was achieved in three steps (9% overall yield[9]) (see Scheme IV-3), while the second synthesis was a biomimetic relay from the natural product, Baikiain (**IV**) in an overall yield of 26% (see Scheme IV-4).[7b]

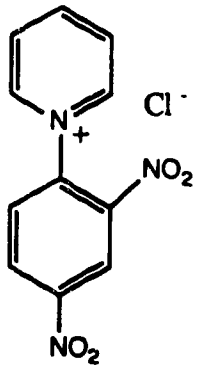


Scheme IV-3

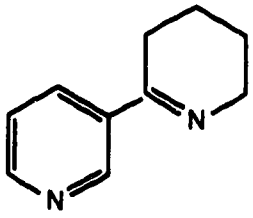


Scheme IV-4

These syntheses yielded racemic anatabine, which is also isolated from tobacco.[3] The most recent synthesis, a stereoselective route starting from Zincke's Salt, V, yielded (+)-anatabine, the enantiomer of the natural product (5 steps, overall yield 6.4%).[10] 2,5-Dihydropyridine-like structures were proposed as transient intermediates in the two of the synthetic routes.[7b,10]



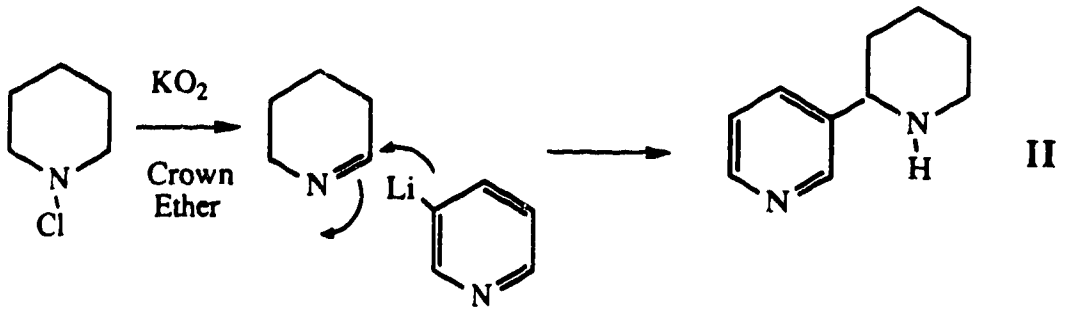
V



VI

Four syntheses of anabasine, II, have been reported.[3,11-13] The first report was the conversion of (-)-anatabine to (-)-anabasine by catalytic hydrogenation.[3] The total synthesis of (±)-anabasine was reported by Alberici and Andrieux[11] starting from cyclopentanone and 3-lithiopyridine. Treatment of the alcohol with hydrazoic acid led to 3,4,5,6-tetrahydro-2,3'-bipyridine (anabaseine), VI. The marine toxin, VI, was converted to (±)-anabasine, II, by $NaBH_3CN$ reduction.

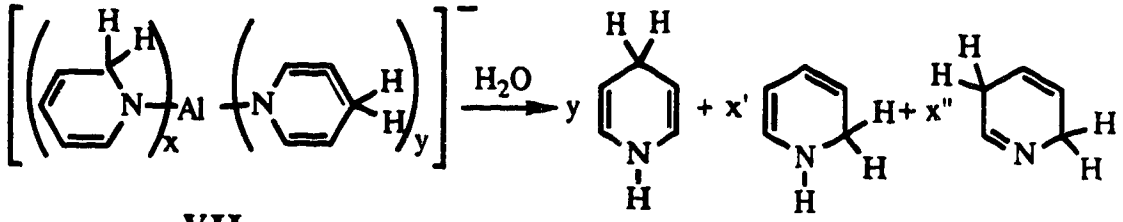
A third synthesis of (±)-II was reported by Scully from the condensation of 3-lithiopyridine with Δ'-piperideine[12](See Scheme IV-5).



Scheme IV-5

An asymmetric synthesis of **II** was achieved after a number of steps starting from the reaction of a chiral template, 2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosylamine, with 3-pyridyl carboxaldehyde.[13]

Dihydropyridines are of interest to both physical organic chemistry and natural product chemistry.[14a] Recently we reported that the hydrolysis, in the absence of oxygen, of lithium tetrakis(N-dihydropyridyl)aluminate (LDPA), **VII**, yields a mixture of three dihydropyridines, **VIII-X**.[14b]



VII **VIII** **IX** **X**

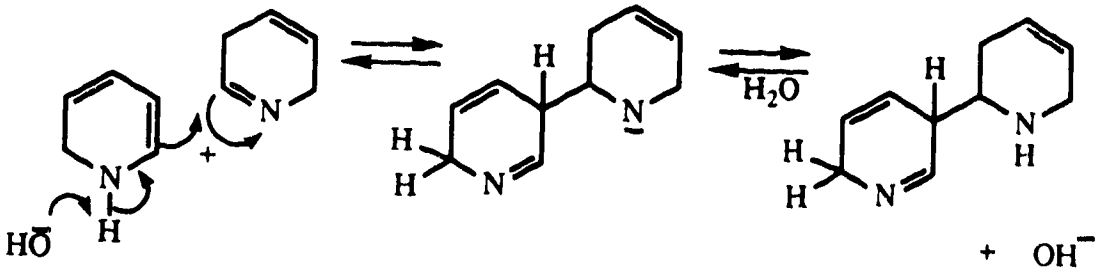
The ratio of 1,4-/1,2-dihydropyridyl ligands in **VII** was dependent on the temperature and the time of "aging" at which **VII** was synthesized.[14b] The aluminate, **VII**, was formed reversibly from LAH and pyridine. LDPA with 1,2-dihydropyridyl ligands is the product of kinetic control while LDPA having 1,4-dihydropyridyl ligands is the product of thermodynamic control. When LDPA was formed by mixing lithium aluminum hydride and pyridine at 0 °C and "aged" for 2 days the average ratio of 1,4-/1,2-dihydropyridyl ligands, y/x, in the isomeric mixture of LDPA's, $\mathbf{VII_{a\text{-}e}}$ ($\mathbf{VII_a}$ x = 4, y = 0; $\mathbf{VII_b}$ x = 3, y = 1; $\mathbf{VII_c}$ x = 2, y = 2; $\mathbf{VII_d}$ x = 1, y = 3; and $\mathbf{VII_e}$ x = 0, y = 4) was 0.35. The LDPA which is formed at 90 °C has a 1,4-/1,2-ratio of ligands of >99. The hydrolysis of LDPA formed at 90 °C yields only 1,4-dihydropyridine while the hydrolysis of the 0 °C preparation yields a mixture of three isomeric dihydropyridines: **VIII**, **IX** and **X** in a ratio of 26:37:38. The ratio of y/(x'+x") was equal to the original 1,4-/1,2- ratio (y/x) of ligands in the LDPA before hydrolysis.[15]

The proposed biomimetic synthesis of anatabine suggested that the natural product Baikiain, **IV**, undergoes decarboxylation to form 2,5-dihydropyridine, **X**, and 1,2-dihydropyridine, **IX**. A condensation of **IX** and **X** presumably yields, after oxidation, anatabine, **I**, see Scheme IV-4. The biosynthetic pathway for the synthesis of **I** suggests that **IX** and **X** are formed from the decarboxylation of 3,6-dihydronicotinic acid (see Scheme IV-1).

Results and Discussion

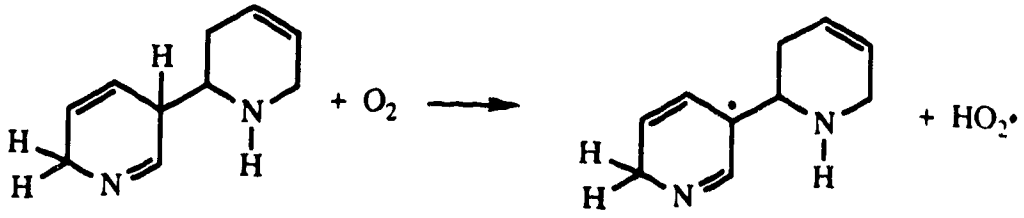
Since the hydrolysate of LDPA (formed at low temperature) yields an almost equimolar mixture of **IX**, and **X**, it was reasonable to suspect that a basic solution (pyridine, $Al(OH)_4^-$) of the hydrolysate would yield, after oxidation, anatabine. The mixture of dihydropyridines, **VIII-X**, was stable in the presence of base (>14 days) and in the absence of oxygen.[14] However, in the presence of oxygen, **I** was slowly formed (~3d). Two mechanistic pathways are suggested: a reversible base catalyzed condensation followed by a radical chain autoxidation, followed by a base catalyzed elimination (Scheme IV-6); or an oxygen catalyzed radical chain dimerization (Scheme IV-7) followed by autoxidation.

Condensation

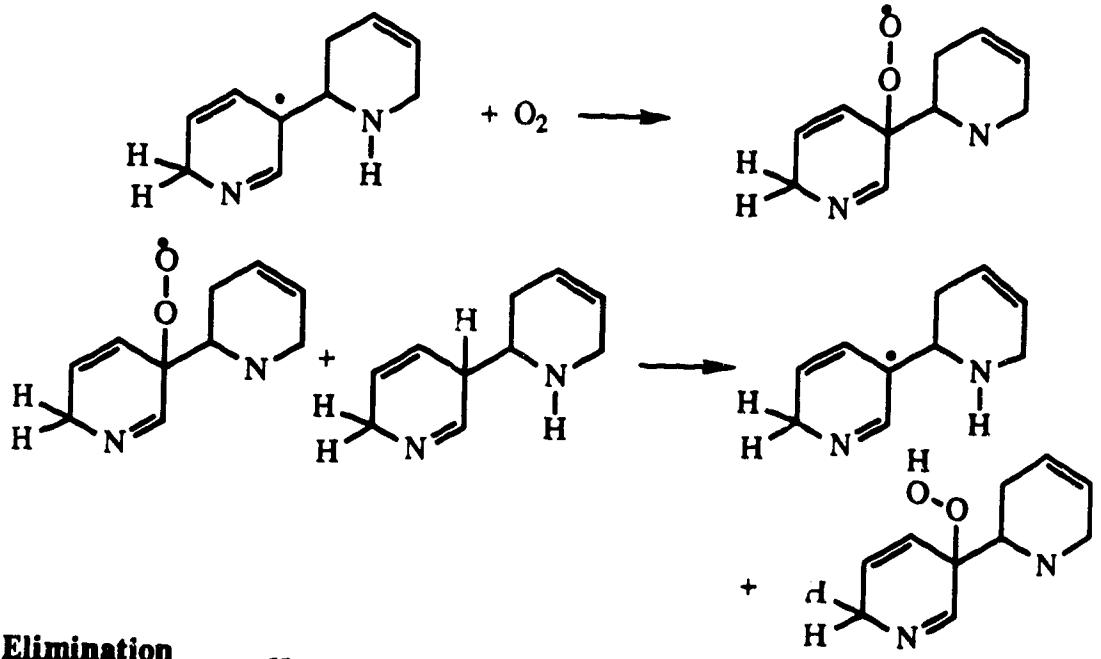


Oxidation

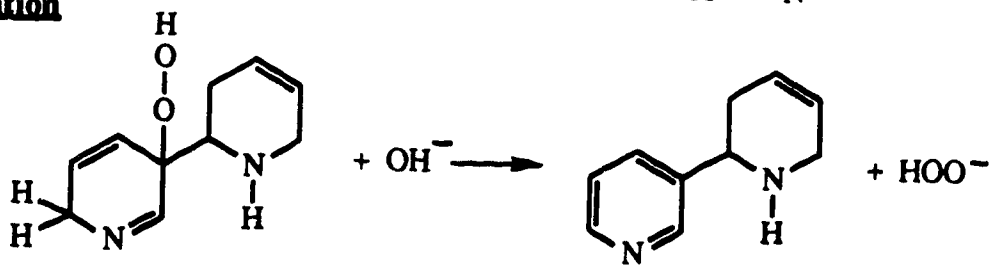
Initiation



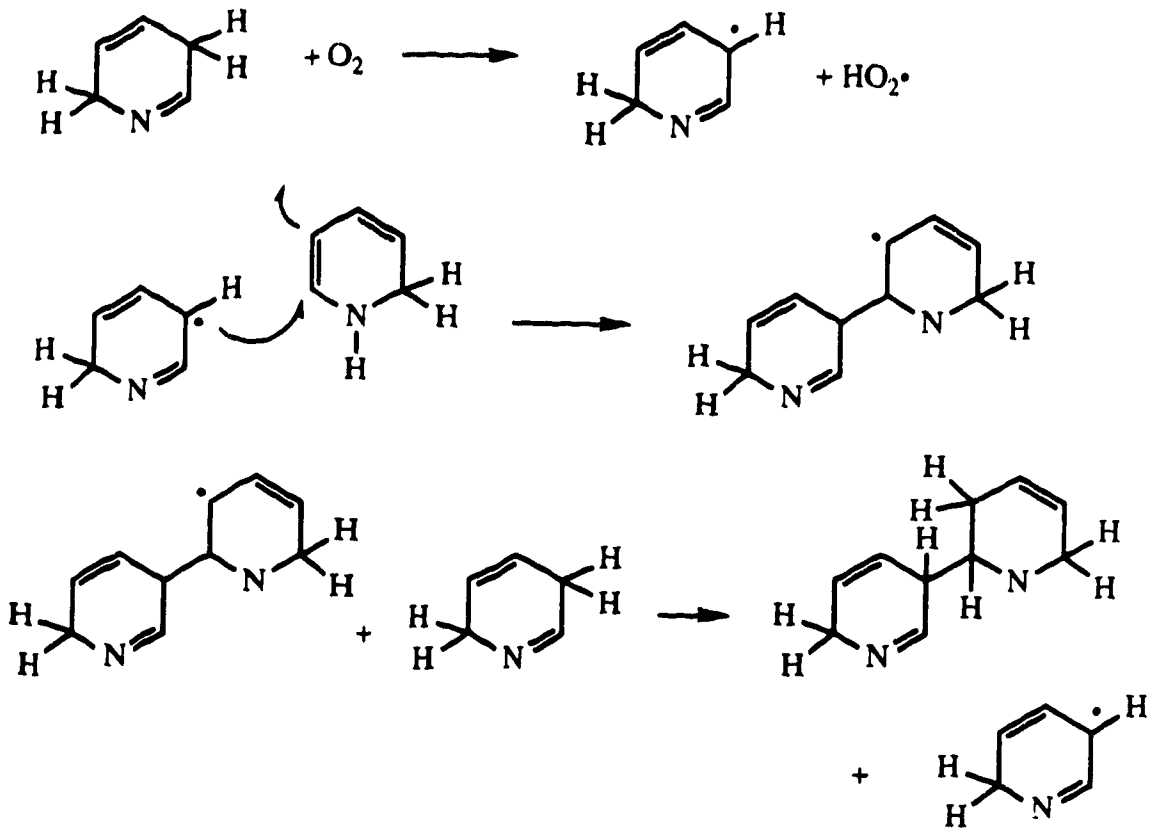
Propagation



Elimination



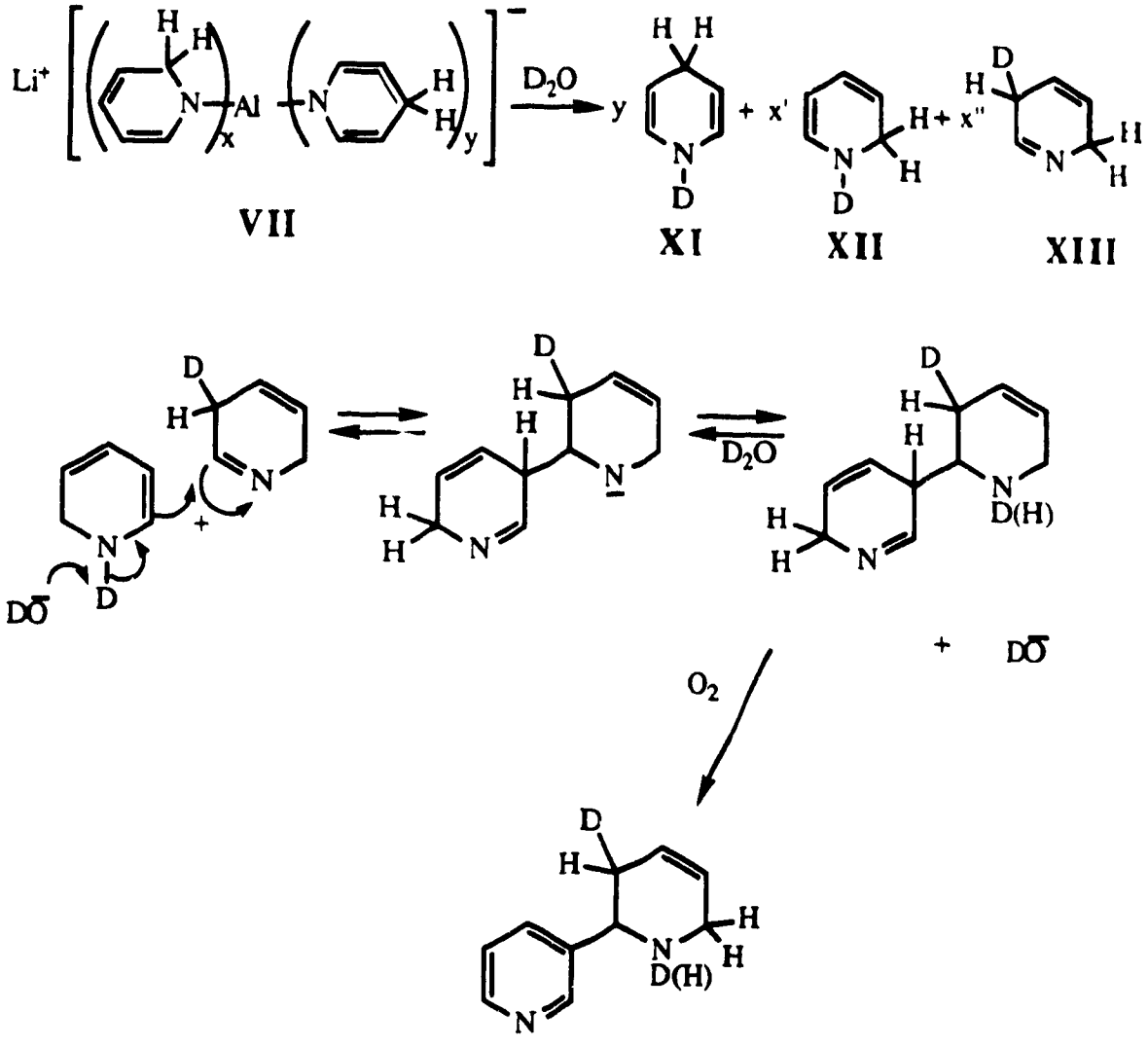
Scheme IV-6



Scheme IV-7

The two proposed condensation pathways were investigated. When LDPA was hydrolyzed in D_2O the 1,4-dihydropyridyl ligands yielded **XI** while the 1,2-ligands yielded **XII** and **XIII** (Scheme IV-8).

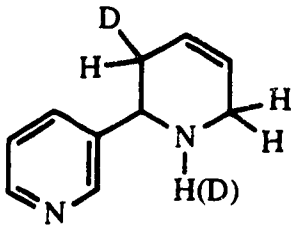
The formation of anatabine from **XII** and **XIII** by the mechanistic pathway in Scheme IV-6 will yield **XIV** (see Scheme IV-8, 9), while its formation by the mechanistic pathway in Scheme IV-7 would yield only **XV** (see also Scheme IV-10), which was actually not observed.



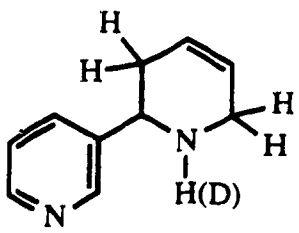
VII XI XII XIII

XIV

Scheme IV-8

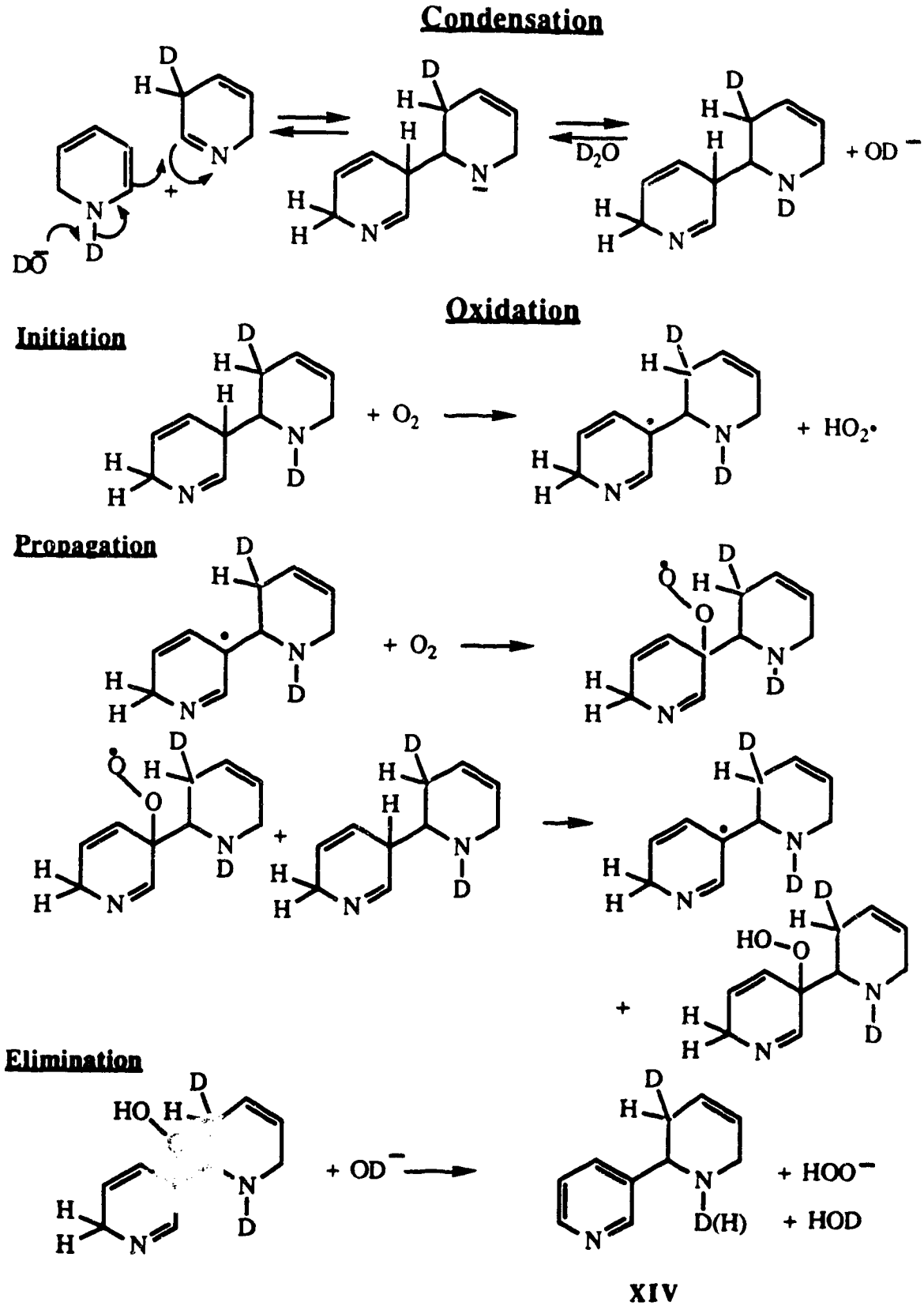


XIV



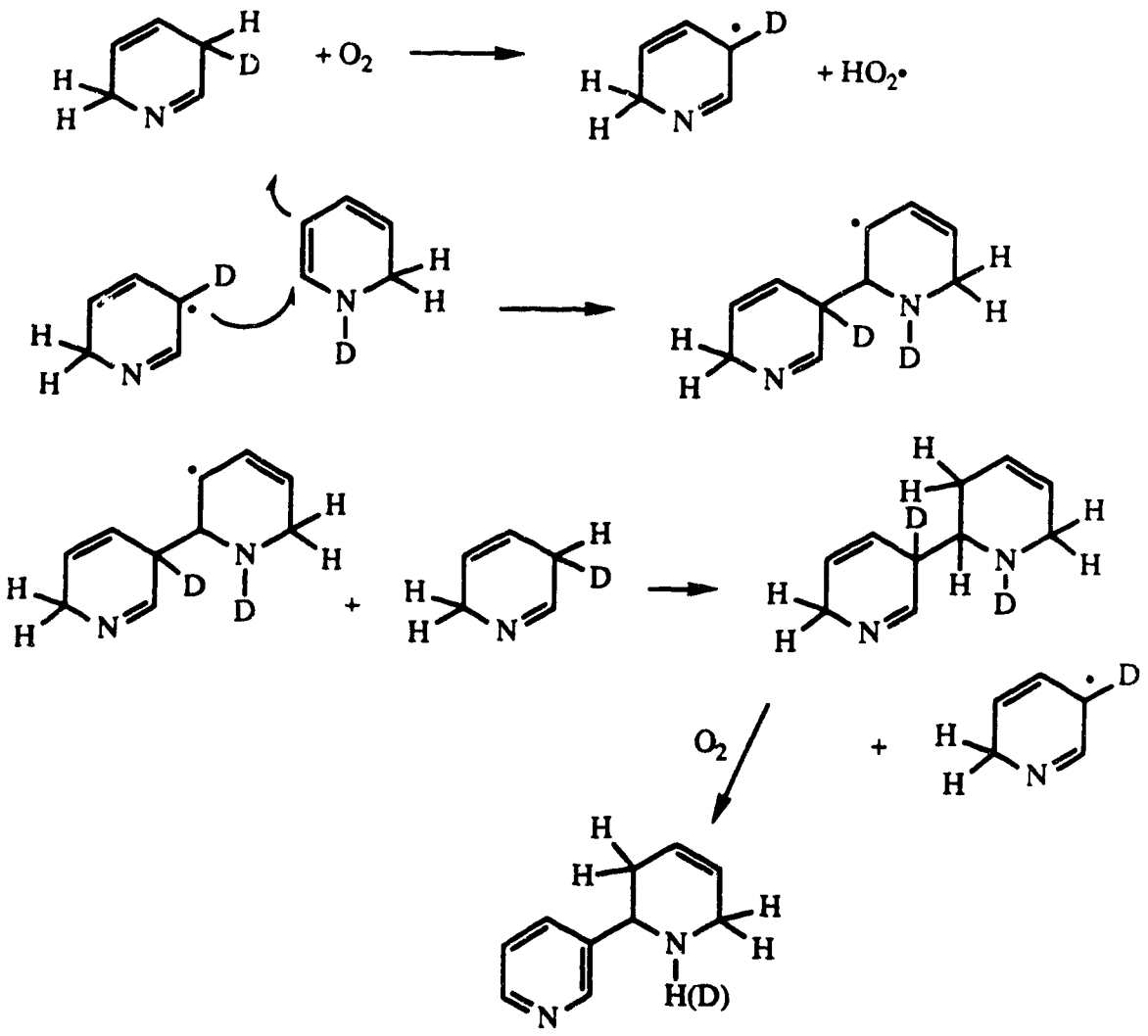
XV

Since only **XIV** is formed from **XII** and **XIII**, the mechanistic pathway in Scheme IV-6 is the most reasonable pathway which describes the synthesis of **I**, see Scheme IV-9.



XIV

Scheme IV-9

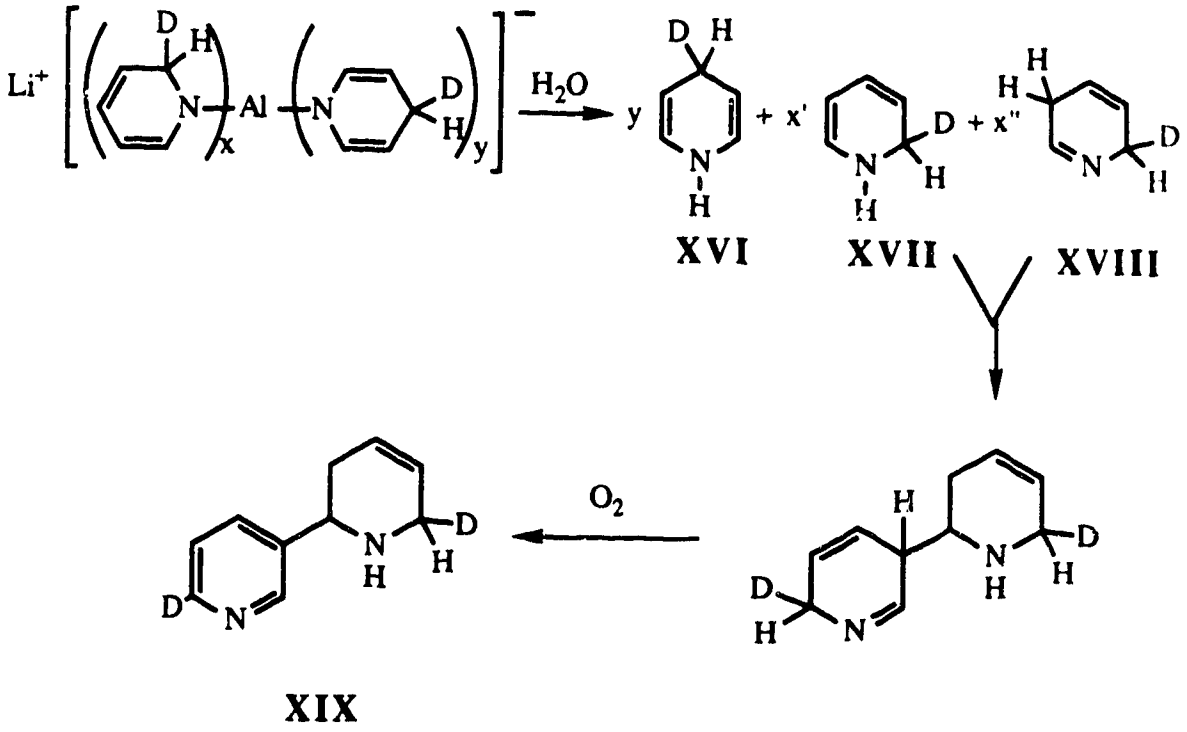


XV

Scheme IV-10

When **VII** is synthesized using $LiAlD_4$ the formed LDPA-d_4 has ligands with 4-deuterated 1,4-dihydropyridyl ligands and 2-deuterated 1,2-dihydropyridyl ligands. Upon hydrolysis, the dihydropyridines formed are deuterated in the 2- and 4-positions. When anatabine is formed from the

deuterated DHP's only 6,6'-dideuteroanatabine (**XIX**) was found, see Scheme IV-11.

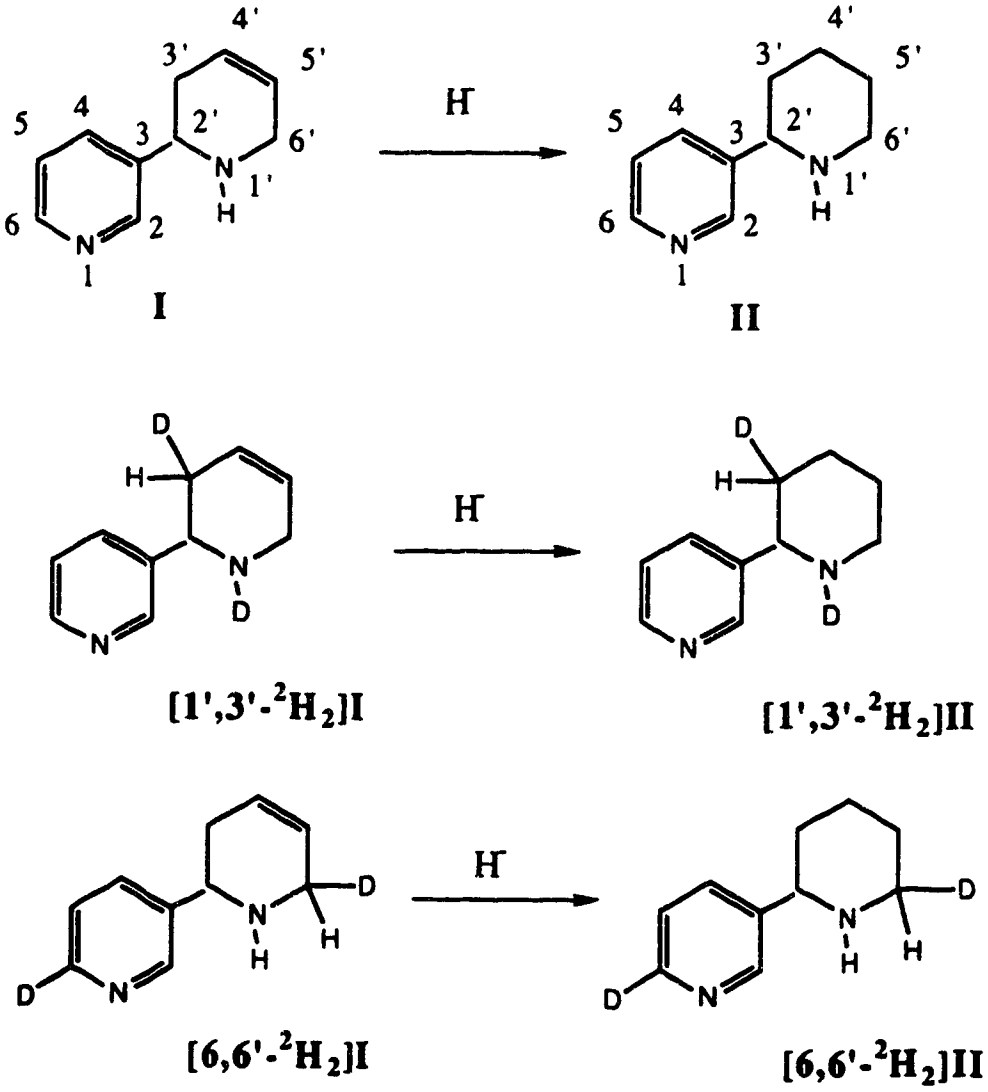


Scheme IV-11

The absence of any 6,4'- or 4,4'-dideuterated **I** clearly rules out the involvement of 1,4-dihydropyridine (**VIII**) in the formation of **I**. The high yield of **I** from the condensation of **IX** (0.68 M) and **X** (0.7 M) attests to the high efficiency of the reaction and confirms that **I** is formed from both **IX** and **X**. If **IX** is used as the limiting reagent, when LDPA is hydrolyzed, then the 59% isolated yield accounts for a near quantitative yield of **I** (89%), *i.e.*, for a 1:1 condensation of **IX** and **X**.[16]

After the mixture of hydrolysates stood at room temperature for more than 3 days during the formation of **I**, a minor amount of anabasine,

II, was formed(~ 10%). Since the LAH and LDPA had been hydrolyzed the only active reducing agents present in the reaction mixture are the three dihydropyridines, **VIII-X**. Presumably these hydride reagents are responsible for the reduction of **I** and the formation of **II**, see Scheme IV-12.



Scheme IV-12

Experimental

Materials - Pyridine (certified reagent grade, ACS or Carledon Laboratories Ltd.) was freshly distilled over barium oxide and potassium hydroxide pellet prior to use. **Lithium Aluminum Hydride** (General Intermediates of Canada) was purified by recovering from diethyl ether after filtration.[14] **D_2O** (99.8%, General Intermediates of Canada), and **Lithium Aluminum Deuteride** (Aldrich, 98% atom D) was used as supplied.

Instrumentation - The ^1H, ^2H, and ^{13}C NMR spectra were obtained using either a Bruker AM-400 (400 MHz) or Bruker AM-300 (300 MHz) NMR spectrometer. Unless otherwise noted the ^1H NMR spectra are referenced to tetramethylsilane as an internal standard at δ 0.00 or $CHCl_3$ as an internal standard at δ 7.26. The ^{13}C NMR chemical shifts are reported in δ (ppm) relative to chloroform (δ $CDCl_3$ = 77.0). The ^{13}C spectra were studied by APT (attached proton test) to determine the number of protons attached to each carbon.

High-resolution mass spectra were obtained with a KRATOS MS50 high-resolution EI^+ mass spectrometer connected to a DS 55 data system. GC analysis was performed with a HP 5840A gas chromatograph equipped with a hydrogen flame ionization detector using a stainless steel column 15 ft × 1/4 inch packed with 10% SE-30 on Chromosorb W (100-200 mesh) and interfaced with a HP5840A integrator.

GC/IR analysis was performed using a HP-5965 GC/FTIR analytical system; GC/MS was run using VG 70E mass spectrometer interfaced to a 11-250 data system.

Unlike the biosynthetic pathway to anabasine, II, the precursor of II in this work must be anatabine. The saturated alkaloid, II, formed at the expense of I was only detected after the reaction mixture which formed anatabine was left to stand for an extended period of time(>3 d). The hydride-reducing agent (*i.e.*, dihydropyridines) was no doubt involved in the formation of II from I.

The Synthesis of Anatabine, I - A pyridine solution of LDPA or tetradeutero-LDPA (0.5 or 0.45 M) was treated with H_2O or D_2O.[14] While the solution was stirred (3 days) at room temperature, and while it was exposed to atmospheric oxygen the solution was analyzed periodically by GC (10% SE-30 on Chromosorb W).[17] After 3 days, chloroform was added to dilute the slurry and the solution was filtered through sintered glass. After filtration the solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of chloroform/methanol/concentrated ammonium hydroxide (90:10:1)[7b] and subjected to silica gel chromatography. The eluate was subjected to vacuum distillation and an isolated yield of 59% was achieved.

(±)-Anatabine - b.p. 116-117 °C/1 mmHg (lit.[3] bp 145-156 °C/10 mmHg), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, 1H, $J_{2'4'}$ = 2.0 Hz, H-2'), 8.42 (dd, 1H, $J_{6'5'}$ = 5.0, $J_{6'4'}$ = 1.8 Hz, H-6'), 7.67 (dt, 1H, $J_{4'5'}$ = 8.0, $J_{4'6'}$ = 1.8, $J_{4'2'}$ = 2.0 Hz, H-4'), 7.20 (ddd, 1H, $J_{4'5'}$ = 8.0, $J_{5'6'}$ = 5.0,

$J_{5'2'}$ = 0.8 Hz, H-5'), 5.78 (A of AB type, 1H, J_{AB} = 10.0 Hz, H-4), 5.72 (B of AB type, 1H, J_{AB} = 10.0 Hz, J_{56ax} = 4.0 Hz, J_{56eq} = 2.0 Hz, H-5), 3.80 (t, 1H, J_{23} = 7.0 Hz, H-2), 3.53 (dm, 1H, J_{ae} = 17.0 Hz, J_{56eq} = 2.0 Hz, H-'6 eq), 3.40 (dm, 1H, J_{ae} = 17.0 Hz, J_{56ax} = 4.0 Hz, H-6 ax), 2.22 (m, N-H), 2.18 (m, 2H, H-3).[7b,9,18] ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.35(C-2'), 148.25(C-6'), 139.79(C-3'), 134.17(C-4'), 126.09(C-5'), 124.89(C-4), 123.49(C 5), 55.04(C-2), 45.71(C-6), 33.58(C-3);[5a,7b] EI+ MS, *m/z*+ (relative intensity) 160 (M^+, 100), 159(29), 156(25), 155(16), 149(196), 131(18), 118(12), 107(23), 106(35), 105(42), 95(33), and 54(42); HRMS, *m/z* obsd 160.0996 (M^+, calcd for $C_{10}H_{12}N_2$ 160.1000). IR (Gas phase) v 3043(vs), 2924(s), 2800(s), 1901(w), 1657(w), 1579(m), 1429(s), 1315(m), 1190(m), 1108(s), 1019(m), 946(w), 783(m), and 714(s) cm^{-1}.[19] Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 75.02; H, 7.47; N, 17.39.

(±)-6,6'-Dideuteroanatabine((±)-[6,6'-$^2H_2$]anatabine) - ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, 1H, $J_{2'4'}$ = 2.0 Hz, H-2'), 8.42 (dd, 0.27H, partially deuterated, $J_{5'6'}$ = 5.0 Hz, $J_{4'6'}$ = 1.8 Hz, H-6'), 7.67 (dd, 1H, $J_{4'5'}$ = 8.0, $J_{4'2'}$ = 2.0 Hz, H-4'), 7.20 (d, 1H, $J_{5'4'}$ = 8.0 Hz, H-5'), 5.78-5.65 (AB, 2H, J_{45} = 11.0 Hz, H-4,5), 3.80 (t, 1H, J_{23} = 7.0, H-2), 3.53 (eq) and 3.40 (ax) (two broad singlets, 1H in total, 0.5H for axial, 0.5 H for equatorial, H-6), 2.22 (m, N-H), 2.18 (m, 2H, H-3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.46(C-2'), 148.40(C-6'), 139.80(C-3'), 133.99(C-4'), 126.12(C-5'), 124.96(C-4), 123.38, 123.24, and 122.95(C-5), 55.03(C-2), 45.64, 45.54, 45.43, 45.34, 45.22, 45.14(C-6, -CDH-), 33.60(C-3). ^{2}H NMR ($CHCl_3$, 400 MHz) δ 8.42 (s, 0.75D, D-6'),

7.26 ($CDCl_3$), 3.53 (s, 0.5D, D-6 eq), 3.40 (s, 0.5D, D-6 ax). ^2H NMR (CH_2Cl_2, 400 MHz) δ 8.50 (s, 0.75D, D-6'), 5.32 (CD_2Cl_2), 3.58 (s, 0.5D, D-6 eq), 3.44 (s, 0.5D, D-6'ax). EI^+ MS, *m/z*$^+$ (relative intensity) 162 (M^+, 93), 161(100), 151(21), 132(22), 108(41), 107(63), 106(75), 80(44), and 55(100); EI^+ HRMS (GC/MS, VG 70E) *m/z*$^+$ obsd 162.1120 (M^+, calcd for $C_{10}H_{10}D_2N_2$ 162.1126).

(±)-1',3'-dideuteroanatabine((±)-[1',3'-$^2H_2$]anatabine) - ^1H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, 1H, $J_{2'4'}$ = 2.0 Hz, H-2'), 8.42 (dd, 1H, $J_{6'5'}$ = 5.0, $J_{6'4'}$ = 1.8 Hz, H-6'), 7.67 (ddd, 1H, $J_{4'5'}$ = 8.0, $J_{4'6'}$ = 1.8, $J_{4'2'}$ = 2.0 Hz, H-4'), 7.20 (ddd, 1H, $J_{4'5'}$ = 8.0, $J_{6'5'}$= 5.0, $J_{5'2'}$ = 0.8, H-5'), 5.78-5.63 (AB quartet of multiplets, 5.68 [dm broad, H-4], 5.63 [dm, H-5], J_{AB} = 11.0, 2H), 3.80 (a doublet [J_{23} = 7.0 Hz] covered by a small amount of triplet [J_{23} = 7.0 Hz], H-2), 3.53 (dm, 1H, J_{ae} = 17.0, H-6_{eq}), 3.40 (dm, 1H, J_{ae} = 17.0, H-6_{ax}), 2.22 (m, N-H), 2.18 (m, 1H, H-3). ^2H NMR ($CHCl_3$, 400 MHz) δ 7.26 ($CDCl_3$), 2.22 (m, N-D), 2.18 (s, 1D, D-3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.15(C-2'), 148.12(C-6'), 139.56(C-3'), 133.77(C-4'), 125.94(C-5'), 124.55(C-4), 123.11(C-5), 54.75, 54.68 and 54.61 (C-2), 45.47(C-6), 33.41(-CH_2-, undeuterated C-3), 33.25, 33.00, and 32.79(C-3). EI^+ MS, *m/z*$^+$ (relative intensity) 162 (M^+, 41), 161(100), 160(75), 159(17), 149(12), 145(15), 132(14), 131(24), 118(21), 107(41), 106(65), 105(67), 55(87), and 54(60); EI^+ HRMS (GC-MS, VG 70), *m/z*$^+$ obsd 162.1114 (M^+, calcd for $C_{10}H_{10}D_2N_2$ 162.1126).

(±)-Anabasine from the hydrogenation of (±)-anatabine - (±)-Anatabine (200 mg, 1.25 mmol) in anhydrous ethanol (25 mL) was

hydrogenated over 100 mg Pd/C (50 psi, 2 h, 23 °C). The solution was filtered the solvent evaporated and the crude (±)-anabasine was subjected to column chromatography (silica gel) followed by vacuum distillation, yield 98.5%.

(±)-Anabasine - b.p. 106-108 °C/2 mmHg (lit.[3] b.p. 104-105 °C/2 mmHg) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.58 (d, 1H, J_{42} = 2.6 Hz, H-2), 8.46 (dd, 1H, J_{56} = 4.9, J_{46} = 1.5 Hz, H-6), 7.76 (dt, 1H, J_{45} = 8.0, J_{46} = J_{42} = 1.8 Hz, H-4), 7.25 (dd, 1H, J_{45} = 8.0, J_{56} = 4.9 Hz, H-5), 3.66 (dd, 1H, $J_{2'3'}$ = 11.0, $J_{2'1'}$ = 2.2 Hz, H-2'), 3.25 (ddm, 1H, $J_{5'6'}$ = 11 Hz, H-6'), 2.80 (dt, 1H, $J_{5'6'}$ = 11.0 Hz, $J_{1'6'}$ = 2.9, H-6'$_{ax}$), 1.90-1.50 (m, 7H);[6b,11] ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.55(C-2, 6), 140.15(C-3), 134.59(C-4), 123.63(C-5), 59.75(C-2'), 47.51(C-6'),34.42(C-3'), 25.38(C-5'), 25.06(C-4');[4] EI$^+$ MS, *m/z*$^+$ (relative intensity) 162 (M$^+$, 32), 161(22), 133(40), 119(28), 106(36), 105(45), 92(15), and 84(100); EI$^+$ HRMS, *m/z*$^+$ obsd 162.1155 (M$^+$, calcd for $C_{10}H_{14}N_2$ 162.1153);[20] IR (gas phase) ν 3052(w), 2944(vs), 2864(m), 2803(m), 1575(w), 1428(m), 1322(m), 1112(m), 1020(m), 797(w), and 716(m) cm^{-1}. Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.74; H, 8.62; N, 17.19.

The vapor phase IR (GC/IR) spectrum of the (±)-anabasine formed in the autoxidation reaction of the mixture of the **IX** and **X** was identical to that of the (±)-anabasine obtained from the hydrogenation of anatabine or the GC/IR spectra obtained from the commercial sample.[21]

(±)-6,6'-Dideuteroanabasine ((±)-[6,6'-$^2H_2$]anabasine) - ^1H NMR ($CDCl_3$, 400 MHz) δ 8.58 (d, 1H, J_{24} = 2.6 Hz, H-2), 8.46 (dd, 0.25 H, J_{65} = 4.9, J_{64} = 1.5 Hz, H-6), 7.76 (dd, 1H, J_{45} = 8.0, J_{42} = 1.8 Hz, H-4), 7.25 (d, 1H, J_{45} = 8.0, H-5), 3.66 (t, 1H, H-2'), 3.25 (s, broad, 0.5H, H-6'eq), 2.80 (s, broad, 0.5H, H-6'$_{ax}$), 1.90-1.50 (m, 7H); ^2H NMR ($CHCl_3$, 400 MHz) δ 8.58 (s, 0.75D, D-6), 7.26 ($CDCl_3$), 3.25 (s, 0.5D, D-6'$_{eq}$), 2.81 (s, 0.5D, C-6'$_{ax}$). (It was reported by Robins[6b] that for anabasine, δ 1.52 (H-3'$_{ax}$), 1.75 (H-3'$_{eq}$), 2.76 (H-6'$_{ax}$), 3.15 (H-6'$_{eq}$)) ^{13}C NMR ($CHCl_3$, 100.6 MHz) δ 148.48(C-2), 148.38(C-6), 140.63(C-3), 134.12(C-4), 123.33, 123.19, 123.02(C-5), 59.65(C-2'), 47.40, 47.30, 47.19, 47.11, 46.98, 46.91(C-6'), 34.72(C-3'), 25.51(C-5'), 25.08(C-4'); EI$^+$ MS, *m/z*$^+$ (relative intensity) 164 (M$^+$, 17), 163(14), 162(4), 135(10), 134(11), 133(19), 121(11), 120(10), 119(26), 107(74), 106(100), 105(26), 94(20), 92(12), 86(7), and 85(34); EI$^+$ HRMS, *m/z*$^+$ obsd 164.1277 (M$^+$, calcd for $C_{10}H_{12}D_2N_2$ 164.1284).

(±)-1',3'-Dideuteroanabasine((±)-[1',3'-$^2H_2$]anabasine) - ^1H NMR ($CDCl_3$, 400 MHz) δ 8.58 (d, 1H, H-2), 8.46 (dd, 1H, H-6), 7.76 (dt, 1H, H-4), 7.25 (dd, 1H, H-5), 3.66 (s, 1H, H-2'), 3.25 (dm broad, 1H, H-6'$_{eq}$), 2.80 (m, 1H, H-6'$_{ax}$), 2.16(N-H), 1.90-1.50 (m, 5H); ^2H NMR ($CHCl_3$, 400 MHz) δ 7.26 ($CDCl_3$), 2.17 (bs, N'-D), 1.58 (s, 0.5D, D-3'$_{eq}$), 1.30 (s, 0.5D, D-3'$_{ax}$);[6b] ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.36(C-2), 148.23(C-6), 140.50(C-3), 133.91(C-4), 123.13(C-5), 59.49, 59.42, 59.35(C-2'), 47.35(C-6'), 34.62(C-3' undeuterated), 34.44, 34.23, 34.18, 33.97, 33.92(C-3'), 25.45(C-5'), 24.79, 24.86, 24.75(C-4'); EI$^+$ MS, *m/z*+ (relative intensity) 164 (M$^+$, 27), 163(67), 162(58), 161(18), 135(9),

134(24), 133(66), 121(19), 120(29), 119(53), 107(29), 106(73), 105(74), 95(35), 86(37), 85(100), and 84(66); EI+ HRMS (GC-MS, VG70), *m/z*+ obsd 164.1271 (M^+, calcd for $C_{10}H_{12}D_2N_2$ 164.1284).

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15 In order to maximize the yield of **IX** and **X** the reaction of LAH and pyridine was carried out at 0 °C and aged only for 2 days. The ratios of **IX** to **X** were calculated from the area integration on the ^{1}H NMR spectra of LDPA hydrolysates.

16 The calculation of the concentration of **IX** and **X** was based on the assumption that LAH was converted quantitatively to LDPA (^{27}Al NMR),[14b] and that LDPA was hydrolyzed quantitatively to the three dihydropyridines (^{1}H NMR).[14b]

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CHAPTER 5

The Use of Fragmentation Probes in a Study of the Reduction Reactions of 8-B-4 Complexes[1]

Introduction

Although the mechanism for the reduction reactions of sodium borohydride is generally considered to involve a hydride transfer process[2] several groups have reported that the reduction of alkyl halides proceeds by a homolytic chain reduction mechanism,[3] see Scheme V-1.

$$RX^{\bullet-} \longrightarrow R\bullet + X^- \quad (1)$$

$$R\bullet + BH_4^- \longrightarrow RH + BH_3^{\bullet-} \quad (2)$$

$$BH_3^{\bullet-} + RX \longrightarrow BH_3 + RX^{\bullet-} \quad (3)$$

Scheme V-1

The chain processes were initiated photochemically[3a] or with oxygen (presumably by the formation of a peroxide).[3b]

During the initiated reduction reactions of alkyl halides with tetra-*n*-butylammonium borohydride the EPR spectrum of the intermediate radical anion $H_3B^{-\bullet}$ has been detected.[4]

An EPR study of the reduction of dimesityl ketone, with BH_3 was reported and the spectrum of the ketyl radical ion was observed. The stable radical is proposed to be the product of electron transfer from the borane.[5]

Boranes (or trialkylboranes) are electronically prohibited from serving as electron donors, whereas "ate" reagents, $[R_xBH_y]^- M^+$ ($x + y = 4$), are reasonable electron donors. The trialkyl boranes are excellent Lewis acids and as such are easily transformed into "ate" intermediates by their complexation with donor molecules or ions, and therefore can serve as electron transfer agents.

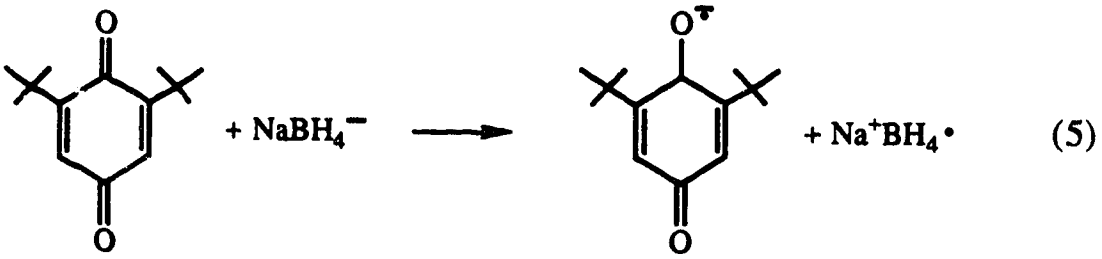
A study by Ashby using several cyclizable probes (6-haloheptene and 5-halocyclooctene) to react with $Li(C_2H_5)_3BH$ was reported and small amounts of cyclized products diagnostic of homolytic reduction were obtained. No chain reduction was reported.[6] These reductions were previously considered to proceed by a hydride transfer mechanism.[7]

Results and Discussion

Reductions by $NaBH_4$ - Treatment of either bromotriphenylmethane, **I**, or 2,5-di-*t*-butylquinone, **II**, with THF solutions of $NaBH_4$ give EPR spectra of the persistant trityl radical (see Fig. V-1) or the ketyl radical ion of the quinone. It was obvious that under these conditions electron transfer from the "ate" complex to acceptors, **I** or **II**, produced their stable radical anions, see eqs 4 and 5. The radical anions were characterized by comparison of their EPR spectra with those previously reported.[8,9]

$$\underset{\textbf{I}}{Ph_3CBr} \rightleftharpoons Ph_3C^+Br^-$$

$$Ph_3C^+ + BH_4^- \longrightarrow Ph_3C\bullet + BH_4\bullet \qquad (4)$$



(5)

II

A fragmentation probe diagnostic of homolytic reduction, the reductive displacement of a *t*-aliphatic nitro compound,[10] was examined using $NaBH_4$.

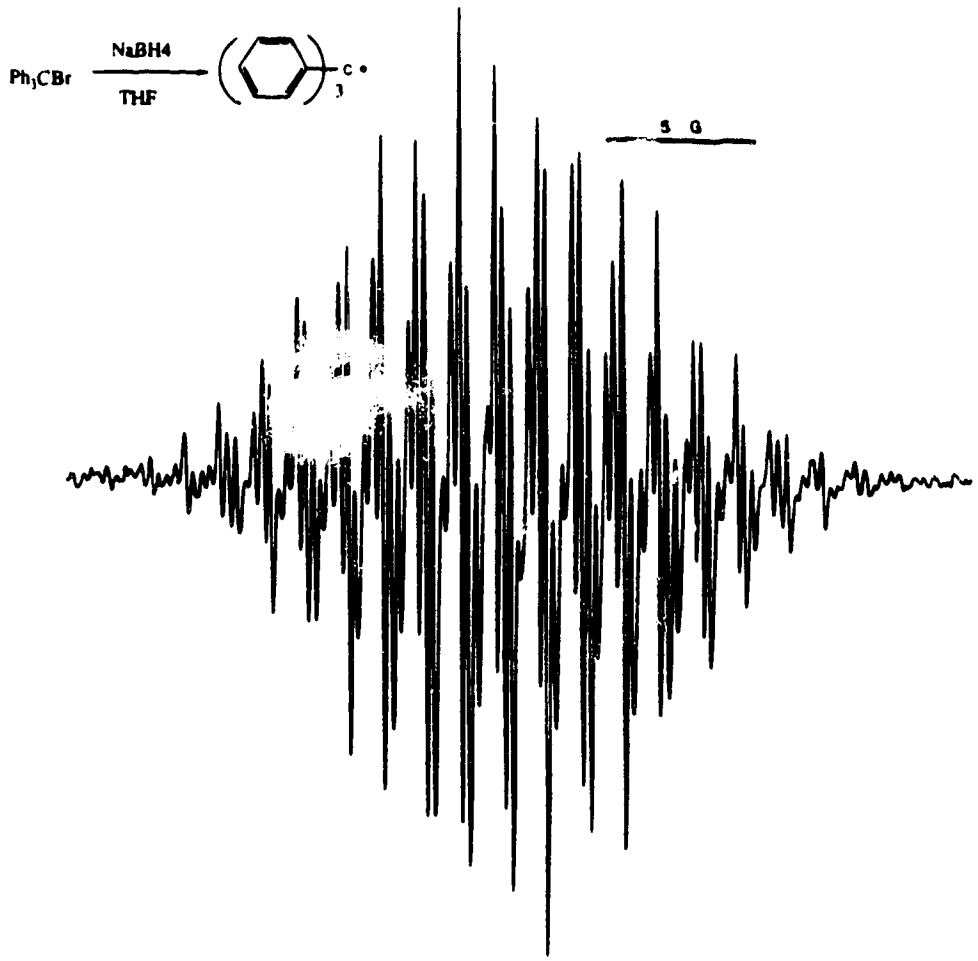
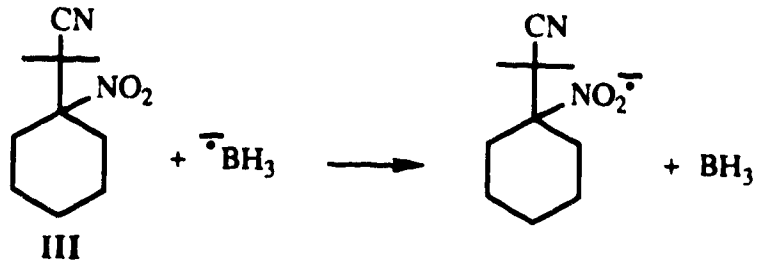
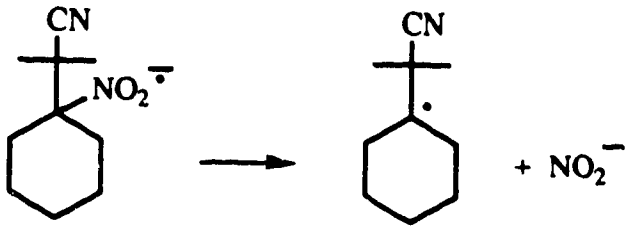


Fig. V-1. EPR Spectrum Obtained from a reaction of $NaBH_4$ with bromotriphenylmethane in THF.

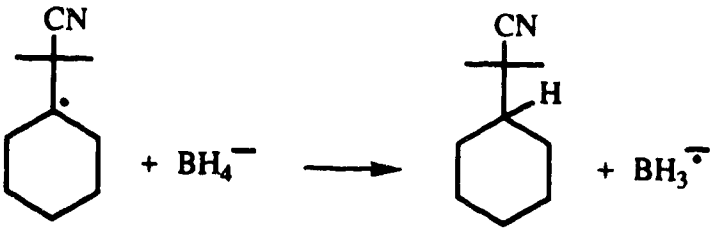
The chain mechanism for the homolytic displacement of NO_2^- from a nitroalkane can be classified as either an electron transfer-fragmentation or an addition-β-scission process. Only the activated nitroalkanes appear to follow the latter pathway.[10] The reduction of 2-(nitrocyclohexyl)isobutyronitrile, **III**, took place in acetonitrile or DMF solvent (23 °C, or 61 °C, 48 h) to give 2-(cyclohexyl)isobutyronitrile, **IIIa**, (see Scheme V-2, eqs 6-8 or 8-10).



III (6)

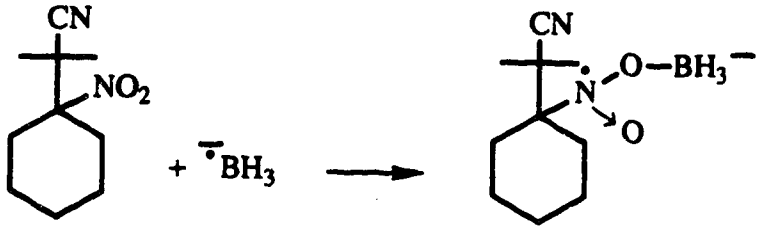


(7)

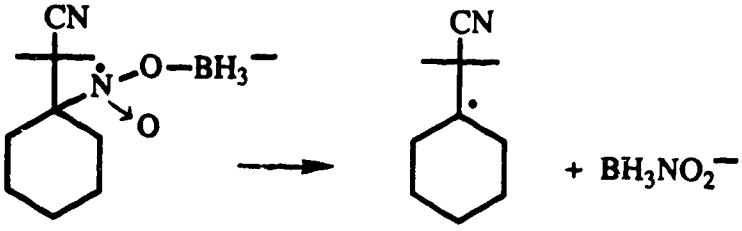


IIIa (8)

or



(9)



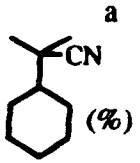
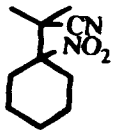
(10)

Scheme V-2

The reaction is typical of a homolytic chain process since it could be initiated with small amounts of AIBN, see Table V-1. The yield of reduction product was not affected by molecular oxygen. Since it was not clear that an electron transfer process was involved in the chain reduction by $NaBH_4$, a more definitive reaction was chosen as a diagnostic probe.

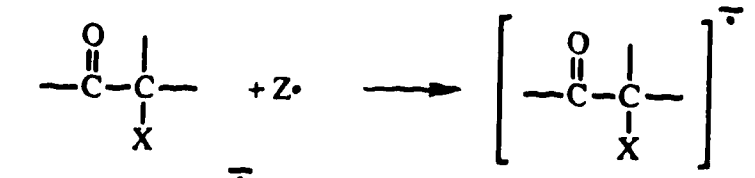
The use of α-haloketones[11a,12b] or ring substituted aromatic ketones[12a] as mechanistic probes has been used successfully to differentiate between the reduction mechanisms which involve either a homolytic electron transfer-hydrogen atom abstraction chain (eqs 11-13 or 15-17) or a heterolytic hydride transfer pathway (eqs 14 or 18),[11] Scheme V-3.

Table V-1. Reduction of 2-Nitrocyclohexylisobutyronitrile (III) with Sodium Borohydride (61 °C).

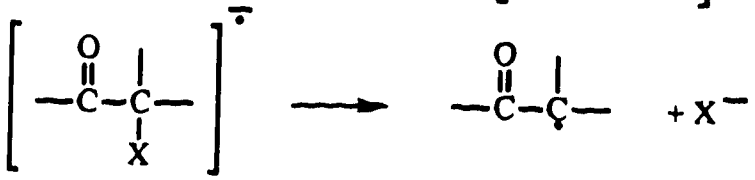
Reaction	$[NaBH_4]/[RNO_2]$	Solvent	Conditions	 (%)[a]	
1	10	CH_3CN	68 h	10±1	78±2
2	10	CH_3CN	48 h, 5% AIBN	56±2	21±2
3	5	DMF	48 h	23±2	69±2
4	5	DMF	48 h, O_2	20±1	79±1
5	5	DMF	48 h, 3% AIBN	36±2	54±1
6	5	DMF	48 h, 5% AIBN	46±2	50±2
7	2.5	DMF	48 h, 5% AIBN	30±0.5	67±0.5
8	20	DMF	48 h, 5% AIBN	63±1	35±2
9	5	DMF	48 h, 5% AIBN, O_2	26±2	65±4
10	10	DMF	48 h, 10% AIBN	67±1	29±1

[a] GLC yields average of 2-3 duplicate reactions. The product is identified by GLC retention times and by a comparison of their GC/IR and GC/MS spectra with those of authentic samples.

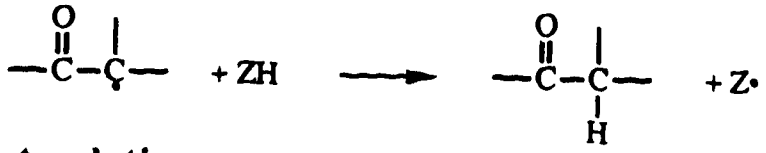
Homolytic



(11)



(12)



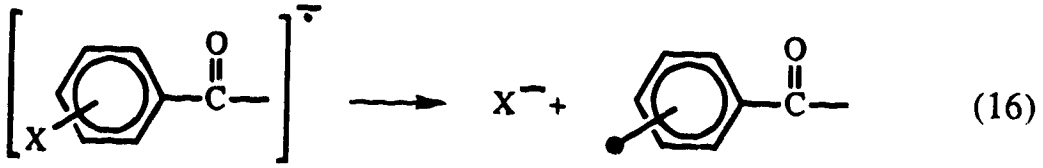
(13)

or **Heterolytic**

(14)

Homolytic

(15)



(16)

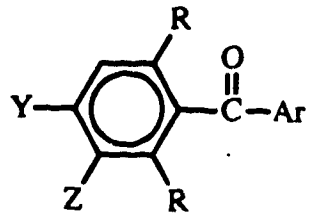
(17)

or **Heterolytic**

(18)

Scheme V-3

These probes can be used to differentiate the mechanism qualitatively on the basis of the products formed or quantitatively on the basis of the rates of fragmentation of the intermediate ketyls.[12a,b] Ketyl fragmentations amenable to study the reduction reactions of 4-B-8 complexes are the ring substituted aromatic ketones, **IVa-c**.



IVa-c

IVa Ar = Ph; Z, R = H; Y = Br
IVb Ar = Mes; Z, R = H; Y = Br
IVc Ar = 3-Br-Mes; Y, R = CH_3; Z = Br

The sodium borohydride reductions of 4-bromobenzophenone (**IVa**) yielded small amounts of the homolytic dehalogenated reduction products when THF solutions of $NaBH_4$ were allowed to react with the halogenated probes, see Table V-2

Since homolytic reduction reactions are involved in the reactions of **I, II, III** and **IVa** and since other substrates have also been implicated in borohydride reductions[3,11] a proposal can be made, and tested, that apparently two mechanistic pathways are open for borohydride reductions, one homolytic and one heterolytic. The major reaction pathway which dominates these competitive reactions is dependent upon the structure of the substrate and/or the reagent; good electron acceptors (**I** and

Table V-2. Reduction of Some Bromodiaryl Ketones (IVa-[illegible]) with $NaBH_4$.

Substrate	Conditions	Additives	Products, %			(Substrate)[c]
			PhCOPh	PhCH(OH)Ph	4-$BrC_6H_4CH(OH)Ph$	(IVa)
VIa[a]	THF, 61 °C, 24 h	-	trace	2.7 ± 0.3	86.4 ± 4.1	10.9 ± 0.5
		AIBN (6%)	trace	4.1 ± 0.5	87.2 ± 4.0	8.7 ± 0.3
	DMF, 61 °C, 24 h	-	0.0	2.8 ± 0.2	92.4 ± 3.5	0.0
		AIBN (6%)	0.0	39.8 ± 1.9	57.4 ± 2.2	0.0
			PhCOMes	PhCH(OH)Mes	4-$BrC_6H_4CH(OH)Mes$	IVb
IVb	THF/C_2H_5OH,[b] 23 °C, 24 h	-	2.8 ± 0.3	4.8 ± 0.4	91.2 ± 3.9	0.0
	THF/C_2H_5OH, 61 °C, 24 h	AIBN (6%)	3.15 ± 0.2	7.78 ± 0.3	92.77 ± 4.6	0.0
		m-DNB (6%)	0.0	2.3 ± 0.3	102 ± 3.8	0.0
	THF, [illegible]	-	1.1± 0.1	0.0	20.5 ± 0.5	78.4 ± 3.7
		[illegible]N (6%)	1.2 ± 0.1	8.6 ± 0.3	16.0 ± 0.4	74.7 ± 3.5
		[illegible]-DNB (6%)	trace	0.0	18.5 ± 0.3	82.5 ± 4.5
	DMF, 61 °C, 24 h	-	3.3 ± 1.9	1.4 ± 0.1	28.2 ± 1.2	66.7 ± 3.4
		AIBN (6%)	23.2 ± 1.4	18.1 ± 1.0	26.2 ± 1.7	30.3 ± 2.1
		m-DNB (6%)	1.1 ± 0.2	0.5 ± 0.1	31.3 ± 1.9	65.4 ± 3.3

Continued.....

Table V-2. (Continued)

Substrate	Conditions	Additives	Products, %		(Substrate)[e]
			MesCOMes	3-BromoMesCOMes	IVc
IVc	DMF,[c] 61 °C, 60 h	-	6.6 ± 0.2	12.5 ± 0.4	80.9 ± 3.9
		AIBN (6%)	104 ± 6.0	0.0	0.0
		m-DNB (6%)	trace	2.36 ± 0.1	95.8 ± 3.7
	C_2H_5OH,[d] 61 °C, 60 h	-	0.0	9.6 ± 0.4	92.5 ± 4.5
		AIBN (6%)	67.9 ± 1.5	30.7 ± 1.0	0.0
		m-DNB (6%)	0.0	0.0	106.0 ± 5.0

[a] [IVa] = 0.025 M; [$NaBH_4$] = 0.072 M. [b] THF/C_2H_5OH:1/1 v/v; The cosolvent was used to increase the solubility of $NaBH_4$. [c] In DMF, [IVc] = 0.0149 M, [$NaBH_4$] = 0.148 M. [d] In C_2H_5OH, [IVc] = 0.0136 M, [$NaBH_4$] = 0.136 M. [e] Unreacted substrates.

II) proceed by the homolytic path while in general most reduction processes proceed by hydride transfer.

For a number of metal hydride reductions Ashby has used as substrates hindered aromatic ketones, mesityl phenyl ketone and dimesityl ketone, as chemical probes which, upon electron transfer, give long lived EPR active ketyl radical ions.[5,13] The rate of hydride transfer is slowed by steric hindrance[14] and the homolytic path becomes more important. The observation of EPR spectra during the course of these reactions, however, is not sufficient evidence for the conclusion that the major reduction products are formed homolytically, since both paths are always available and only traces of ketyl radical ions will give persistent EPR absorption.

With the hindered probe, **IVb**, reactions of THF/ethanol, THF, and DMF solutions of $NaBH_4$ show products diagnostic of both homolytic and heterolytic reduction pathways. The homolytic dehalogenated products are only formed from a minor process. Heterolytic reduction can be initiated by AIBN and inhibited by small amounts of DNB, see Table V-2.

With an even more hindered probe, **IVc**, although the reaction is very sluggish, reaction in solvents C_2H_5OH or DMF give only homolytic reduction products, see Table V-2.

Reductions by $Na(C_2H_5)_3BH$ - When the reductions of **IVa-c** were carried with $Na(C_2H_5)_3BH$ under the same conditions used for $NaBH_4$ the reactions gave almost identical amounts of homolytic reduction, see Table V-3.

The results listed in Table V-3 are consistent with both of the conflicting studies of the mechanism of $NaB(C_2H_5)_3H$ reductions

Table V-3. Reductions of Bromoaryl Aryl Ketones (**IVa-c**) with $NaBEt_3H$.

Substrate	Conditions	Additives	Products, %			(Substrate)[e]
			PhCOPh	PhCH(OH)Ph	4-BrC_6H_4CH(OH)Ph	(IVa)
IVa[a]	THF, 61°C, 24 h	-	trace	2.3 ± 0.2	88.5 ± 4.2	9.2 ± 0.4
		AIBN (6%)	1.4 ± 0.2	2.6 ± 0.2	90.2 ± 3.9	5.8 ± 0.2
		m-DNB (6%)	0.0	0.7 ± 0.1	89.4 ± 3.8	9.9 ± 0.8
			PhCOMes	PhCH(OH)Mes	4-BrC_6H_4CH(OH)Mes	IVb
IVb	THF,[b] 23°C, 15 h	-	2.0 ± 0.1	4.8 ± 0.3	61.9 ± 3.0	35.0 ± 2.6
	THF, 61°C, 4 h	-	2.4 ± 0.1	8.3 ± 0.8	60.6 ± 3.1	23.9 ± 2.0
	THF,[c] 61°C, 24 h	-	2.4 ± 0.2	10.1 ± 0.4	82.2 ± 3.7	0.7 ± 0.2
		AIBN (6%)	2.1 ± 0.1	11.2 ± 0.4	85.7 ± 3.9	0.4 ± 0.2
		m-DNB (6%)	0.0	trace	≥99.8 ± 2.0	0.0
			MesCOMes	3-BromoMesCOMes		IVc
IVc[d]	THF, 23°C, 24 h	-	0.0	3.0 ± 0.2		95.0 ± 3.7
	THF, 23°C, 22 h	-	trace	16.7 ± 1.0		87.7 ± 2.8
		AIBN (6%)	0.9± 0.1	28.5 ± 2.4		73.8 ± 2.0
		m-DNB (6%)	0.0	4.6 ± 1.1		96.5 ± 3.2

[a] [**IVa**] = 0.025 M, [$NaBEt_3H$] = 0.50 M. [b] [**IVb**] = 0.024 M, [$NaBEt_3H$] = 0.250 M. [c] [**IVb**] = 0.024 M, [$NaBEt_3H$] = 0.050 M. [d] [**IVc**] = 0.0046 M, [$NaBEt_3H$] = 0.044 M. [e] Unreacted substrates.

previously reported.[6,7] The study reported by Ashby[6] concluded that a SET pathway was responsible for the reduction reactions of alkyl halides with $NaB(C_2H_5)_3H$. These conclusions were based on the observation that very small amounts (1-4%, 0 °C; 11%, -78 °C) of cyclized 5-membered ring product were formed during the reduction of 6-iodoheptene, and that the trityl radical was observed (EPR) when trityl bromide was allowed to react with a THF solution of $NaB(C_2H_5)H$. The observation of small amounts of products indicative of a radical reaction does not define the major pathway and, as is the case of the reductions of **IVa**, it appears that only very minor amounts of homolytic products are formed. Furthermore, it has been suggested that only trace amounts of radicals can produce cyclized products in these systems by a chain mechanism that does not involve the nucleophilic reagent in the chain propagating step.[15]

Since the reactions of trityl bromide with $NaBH_4$ give an EPR spectrum of the trityl radical it appears that the borate does undergo SET with very good acceptors (trityl carbonium ion). Since the EPR technique is so sensitive (10^{-7}–10^{-8} M) again only small amounts of the reduction product may be formed by a homolytic pathway.

The reduction of the most hindered ketone, **IVc**, with $NaB(C_2H_5)H$ was extremely sluggish, but only homolytic reduction products were detected. The reduction (THF, 61 °C, 22 h) could be initiated with AIBN and inhibited with DNB. No product from hydride transfer was formed.

Although small amounts of radical products are involved in the reduction of most substrates with $NaB(C_2H_5)_3H$, the conclusions reached by Brown,[7] that the major pathway for $NaB(C_2H_5)_3H$ reduction involves a hydride transfer reaction is probably correct. In special cases, such as in

the reduction of an extremely hindered ketone, **IVc**, the hydride transfer process is so slow that only the homolytic pathway occurs.

Reductions with Lithium Dimesityl Borohydride ($LMBH_2$•2DME), V - Since the more hindered substrates gave more homolytic reduction it was assumed that a more hindered reagent[21] would likewise show more homolytic reduction. As expected, when $LMBH_2$•2DME, **V**, was allowed to react with **IVb**, the reaction yielded only homolytic dehalogenation reduction products, see Table V-4.

Although the reaction was very sluggish it was shown to proceed via a short chain radical process since it could be inhibited by a small amount of DNB. The hindered reagent, unlike $NaBH_4$ which reacts with **IVb** primarily by hydride transfer, gave only products which are diagnostic of an electron transfer-hydrogen atom abstraction process. The radical chain reduction reactions of **V** were further substantiated by carrying out the reductions of **IVb** in solvent DMF. At 61 °C the reaction yielded 4% homolytic reduction product, while with small amounts of AIBN (4%), 32% of the radical chain process was produced, see Table V-4.

A facile SET process between **V** and **I** or **II** was demonstrated to occur with these good electron acceptors. With **I** an immediate spectrum of the trityl radical was obtained when a degassed THF solution of an equimolar mixture of **V** and **I** were mixed in the cavity of an EPR spectrometer. When $LMBH_2$ was allowed to react with a DME solution of **II** the EPR spectrum of the spin adduct of **II** was immediately obtained. The structure of this persistent radical adduct was consistent with the triplet splitting, of the the two quinone hydrogens and the doublet splitting attributed to the hydrogen atom on boron.

Table V-4. The Reduction of $LMBH_2 \cdot 2DME$ with Several Mechanistic Probes.[a]

Substrate	Conditions	Products (%)			SM (%)
		$PhCH(OH)CH_2Cl$	$PhCH\overset{O}{\diagdown\diagup}CH_2$	$PhCH_2CHO$	
$PhCOCH_2Cl$	DME 23 °C, 2h	40	60	0	0
	1. DME, 23 °C, 2h; 2. H_2O, 24 h	0	66	33	0
		$4\text{-}BrC_6H_5CH(OH)CH_3$			
$4\text{-}BrC_6H_5COCH_3$	2 h	79			21
		$4\text{-}BrC_6H_5CH(OH)Ph$			
$4\text{-}BrC_6H_5COPh$ (**IVa**)	2 h	82			18
		$PhCOMes$			
$4\text{-}BrC_6H_5COMes$ (**IVb**)	24 h	13			79
	24 h, DNB (1.5%)	0			100
	DMF, 61 °C, 24 h	4			96
	DMF, 61 °C, AIBN (4%)	32			68

[a] The experiments were carried out by Dr. Xie, G.

Conclusions

The reduction reactions of borohydrides proceed by both homolytic and heterolytic pathways. Generally the heterolytic process is the dominant process. When the reducing agent and/or the substrate is sterically hindered a homolytic reduction mechanism is followed. However, when the substrate reduced is a very good electron acceptor the homolytic process should be more important.

Experimental

Instrumentation - ^1H NMR spectra were obtained using either a Bruker AM-400 (400 MHz) or Bruker AM-300 (300 MHz) NMR spectrometer with deuteriochloroform as solvent and residual chloroform (δ 7.24) as an internal lock. EPR spectra were obtained using a Bruker ER200E/SRC spectrometer fitted with a ER4102 ST-Universal X-Band Resonator operated at 9.6 GHz. Gas phase chromatograph/mass spectra (GC/MS) were recorded on a VG-70E mass spectrometer interfaced to a Varian Vista 6000 GC fitted with a DB-1 capillary column interfaced to a 11-250 data system. Gas phase chromatograph/infrared spectra (GC/IR) were obtained with a HP-5965A IRD spectrometer interfaced to a HP5890 gas chromatograph (Hewlett-Packard) that was fitted with a glass capillary column (Hewlett-Packard ultra 2, 25 m x 0.32 mm x 0.52 μ).

Materials - **Tetrahydrofuran** (Aldrich, HPLC grade) was dried over KOH and freshly distilled from Na/Ph_2CO. **Acetonitrile** (Aldrich) was purified by standard procedure[16] and distilled from CaH_2 before use. **Dimethylformamide (DMF)** (Aldrich, HPLC grade) was distilled from CaH_2. **Ethanol** (Quantum) was distilled from MgO.

2-(Nitrocyclohexyl)isobutyronitrile (III) was prepared by the method of Kornblum:[17] mp 108.5-110 °C (lit.[17] 108-109 °C). **2,5-Di-*t*-butylbenzoquinone (II)** (Aldrich, 98%) was used as received (mp 65-67 °C). **Bromotriphenylmethane (I)** (Aldrich, 98%) was recrystallized from benzene/pet. ether mp 153-154.5 °C (lit.[18] mp 152-154 °C); Anal. Calcd for $C_{19}H_{15}Br$: C, 70.60; H, 4.68. Found: C, 70.83; H, 4.70.

α,α'-Azobis(isobutyronitrile) (Aldrich) was recrystallized from ethanol-water, mp 102 °C (lit.[18] mp 103 °C). ***m*-Dinitrobenzene** (Fisher) was recrystallized from methanol, mp 91.5-92 °C (lit.[18] mp 88-90 °C). The internal standard for GC, **1,4-di-*t*-butylbenzene** (Aldrich) was recrystallized from ethanol and dried over P_2O_5 in vacuum at 55 °C, mp 78-79 °C (lit.[18] mp 80 °C).

Sodium borohydride ($NaBH_4$) (BDH) was recrystallized twice from ethylene glycol dimethyl ether (Aldrich) and dried under vacuum.

$Na(C_2H_5)_3BH$ (Aldrich, 1.0 M solution in THF) was used as supplied.

4-Bromobenzophenone (IVa) (Aldrich) was recrystallized from ethanol/pet. ether (30-60 °C), mp 80.5-81.5 °C (lit.[19] mp 80-82.5 °C), Anal. Calcd for $C_{13}H_9OBr$: C, 59.80; H, 3.47. Found: C, 59.60; H, 3.39.

4-Bromo-2',4',6'-trimethylbenzophenone (IVb) was prepared by treating a CS_2 solution of 4-bromobenzoyl chloride with mesitylene in the presence of aluminum trichloride,[20] mp 71.5-72.0 °C (lit.[20] mp 71-72 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 4H), 6.85 (s, 2H), 2.30 (s, 3H), 2.04 (s, 6H). Anal. Calcd for $C_{16}H_{15}OBr$: C, 63.32; H, 5.05; Br, 26.35. Found: C, 63.38; H, 4.99; Br, 26.35.

3,3'-Dibromo-2,2',4,4',6,6'-hexamethylbenzophenone (IVc) was prepared from dimesitylketone (3.2 g, 12 mmol), 20 mL CCl_4, 0.05 g $FeCl_3$ and a piece of I_2. A solution of 1.5 mL bromine (28 mmol) in 10 mL CCl_4 was added dropwise while the mixture was stirred at r t . After 1 h, the mixture was heated at reflux for 4 h. The mixture was then diluted with ether, washed with aqueous 10% $NaHCO_3$ solution, 5% sodium thiosulfate, and finally with water. The solvent was evaporated and white

solid was obtained. After flash chromatography (silica gel, 20-45 μ, pH 7.1) using 5:95 diethyl ether/hexane as eluant and subsequent recrystallization, 2.7 g product (white crystal) was obtained (yield, 52%). GC showed one peak. TLC (Silica gel, 5:95 v/v g Et_2O:hexane) showed one spot: mp 103-104 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 6.90 (s, 2H), 2.36 (s, 6H), 2.25 (s, 6H), 2.00 (s, 6H). Anal. Calcd for $C_{19}H_{20}Br_2O$: C, 53.80; H, 4.75; Found: C, 53.74; H, 4.86. HRMS, m/z^+ 425.9840(Calcd for $C_{19}H_{20}{}^{81}Br_2O$: 425.9840).

Lithium dimesityl borohydride bis(dimethoxyethane), $LMBH_2$•2DME, was prepared according to the literature procedure,[21] mp 164-165 °C (lit.[21] 164-165 °C).

General procedure for the reduction of substrates and quantitative GC analysis of products - An aliquot of a solution of borohydride (0.05-0.25 M in a desired solvent, THF, DMF, CH_3CN, ethanol, or THF/ethanol) was placed into one arm of a Pyrex H tube, an aliquot of a solution of a substrate (0.020-0.025 M, with or without the additive AIBN or DNB) in the same solvent containing 1,4-di-*t*-butylbenzene was placed into the other arm of the H tube. The tube was degassed under vacuum (three times) and sealed. The two solutions were thermostated at the desired temperature and mixed. The reaction was carried out for the time specified, see Tables V-1, 2, 3. The tube was cooled, opened, quenched with dilute HCl, and dried (anhydrous $MgSO_4$). The solutions were analyzed by GC.

The product mixture from the reduction of 4-bromobenzophenone (**IVa**) was analyzed using a 25 ft x 1/4 inch stainless steel column packed

with 10% FFAP on Chromosorb, WAW DMCS, 60/80 mesh. The product mixtures from the reductions of **III**, **IVb**, and **IVc** were analyzed using a 25 ft x 1/4 inch stainless steel column packed with 10% SE-30 on Chromosorb, WAW DMCS, 60/80 mesh. GC analysis was carried out using a HP5840A gas chromatograph equipped with a hydrogen flame detector interfaced to a HP5840A integrator. The area ratios were converted to mole ratios for quantitative determinations by using standard calibration curves constructed from known mixtures of the authentic materials. Products were identified by a comparison of their retention times, GC/MS, and GC/IR spectra with those of authentic materials. The quantitative results listed in Tables V-1, 2, 3 are the average results of two or more independent experiments.

EPR Spectroscopy of the reactions between the borohydrides and bromotriphenylmethane (I) or 2,5-di-t-butylquinone (II) - A THF solution of bromotriphenylmethane (2.0 mL, 0.02 M) or 2,5-di-*t*-butylbenzoquinone was placed in one of the divided arms of a H tube fitted with a quartz EPR tube. A second THF solution of the borohydride (2.0 mL, 0.02 M) was placed in the second arm of the H tube. The solutions were degassed three times, and then sealed. The solutions were mixed at room temperature and the filled EPR tube was immediately placed into the cavity of the EPR spectrometer. The EPR spectrum was then recorded.

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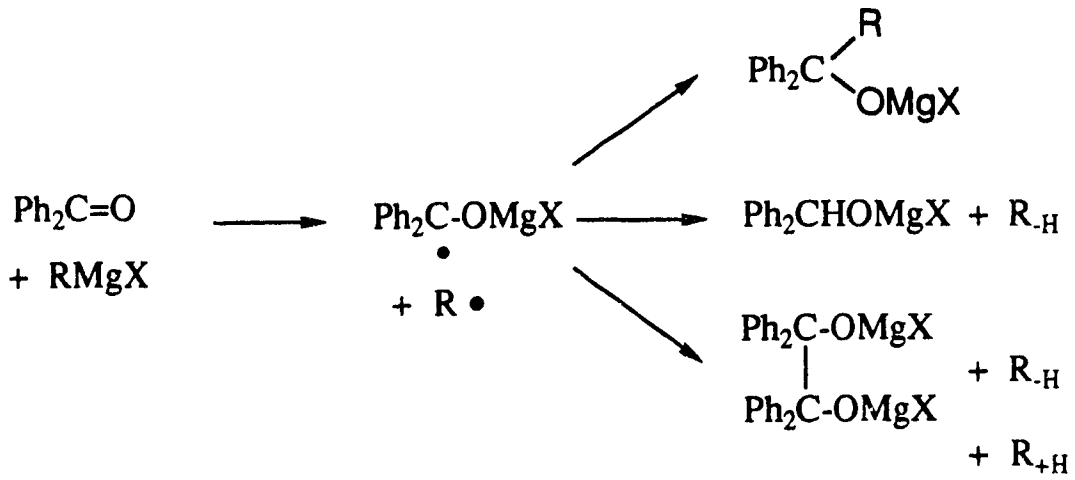
CHAPTER 6

The Single Electron Transfer Pathway for the Reactions of Grignard Reagents with Aromatic Ketones. The Use of the Fragmentation Probe to Calibrate the Reactions[1]

Introduction

The Grignard reaction plays a crucial role in synthetic organic chemistry. The reaction mechanism of the reagent with aromatic ketones has been the subject of several reviews.[2] Because of the polar nature of the carbon-magnesium bond the reactions of the Grignard reagents were first considered to be those of potential carbanions and it was therefore conventionally believed that the reactions of the reagents with aldehydes and ketones proceeded via a polar mechanistic pathway.[3] In 1929 a homolytic reaction mechanism for the Grignard reagent was suggested as a hypothesis by Blicke and Powers[4] to explain its reaction with benzophenone. It was proposed that an alkyl radical and the magnesium salt of benzophenone ketyl was initially formed and the two radicals might combine subsequently to form the 1,2-addition product or possibly, the ketyl would abstract hydrogen from the β-position of the alkyl radical, which would lead to the disproportionation products, benzhydrol and an alkene. It was also suggested that two ketyl radicals might combine to form benzopinacol and that the alkyl radical in this case would disproportionate to form alkene and alkane, Scheme VI-1.



Scheme VI-1

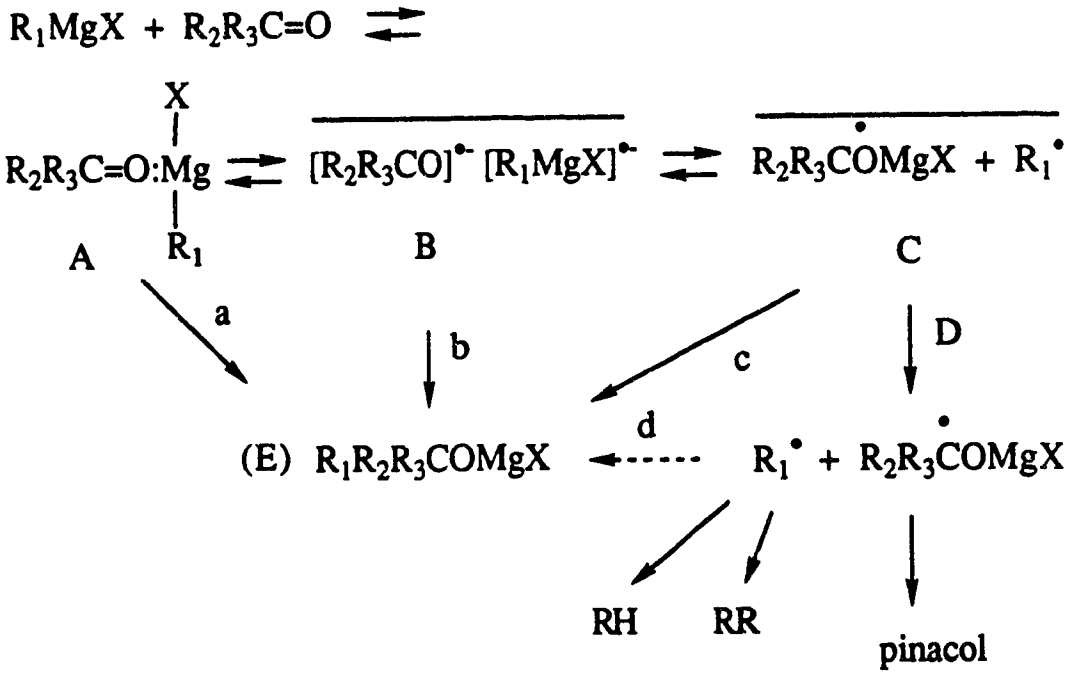
The formation of benzopinacol was reported a few years later by Arbuzov and Arbuzova[5] from the reaction of cyclohexylmagnesium bromide with benzophenone. Since the EPR technique was successfully used to detect the formation of radical species in the reactions of benzophenones and carbanions[6,7], substantial evidence is available that an electron transfer pathway is involved in the Grignard reactions with aromatic ketones.[8] It has been controversial for the past several decades that the Grignard reactions of ketones proceed via polar and/or SET mechanistic pathways, *i.e.*, whether Grignard reagents behave primarily as anion precursors and react by concerted reaction mechanisms and that SET is a minor process, or whether they are electron donors and therefore react by stepwise SET pathways.[8a-c]

The mechanistic arguments are based not only upon the formation of pinacol, but also upon the formation of benzhydrol and the formation of abnormal addition products (*i.e.*, products other than 1,2-adducts). Whereas spectroscopic methods such as EPR and CIDNP are very useful for

detecting the presence of radical intermediates, these methods have inherent drawbacks, since a quantitative estimation of radical concentration is difficult to obtain and the short life-time of the intermediates can lead to the conclusion that radicals are not involved. In addition to the direct EPR spectroscopic observation of radical intermediates which are formed in some Grignard reactions, a number of other techniques[2b] have also been used to elucidate the mechanism of these reactions.

A potential "radical clock" was included in the Grignard reagent, *i.e.*, 5-hexenylmagnesium chloride. The SET reaction of this Grignard reagent was expected to yield cyclized product (cyclopentyl products), an indication that the 5-hexenyl radical is involved. It was reported that during the reaction of 5-hexenylmagnesium chloride with benzophenone or with 2-methylbenzophenone (2-MBP), no cyclized 1,2-addition product was observed. The author[2b] argued that the alkyl radical which is formed couples with the ketyl more rapidly than it cyclizes. A *cis*-enone, as a substrate probe was used since its radical anion has the ability to isomerize to the *trans*-enone if a Grignard reagent transfers an electron to the substrate. Experiments showed that when *t*-butylmagnesium chloride was allowed to react with 100% molar excess of *cis*-enone, most (96%) of the recovered enone isomerized to the *trans*-enone and most of the 1,2-addition product also exhibited *trans* stereochemistry. The conclusion was that isomerizable ketyl anion was an intermediate during the reaction of a 3° Grignard reagent. Radical inhibitors such as *p*-dinitrobenzene (DNB) or other spin traps such as nitroso compounds or nitrones have been used to trap the ketyl and to inhibit the formation of pinacol during the reactions of alkylmagnesium chlorides with 2-MBP.[2b,8a]

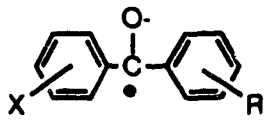
The kinetics of the SET pathway have recently been analyzed by Walling.[10] When typical reaction rates were assumed, the proposed radical mechanism is found to be in reasonable agreement with most of the published experimental results. The kinetic analysis of the mechanism (Scheme VI-2) assumes that the reaction is first order in monomeric Grignard reagent (RMgX) and first order in substrate and that radical-ketyl cross-coupling leads to products which are formed from encounter pairs from outside of the primary solvent cage (step d, Scheme VI-2)



Scheme VI-2

The major questions which initiated Walling's analysis was again whether SET is the sole reaction path or a minor side process. This question is inherent in the analysis of any mechanistic study which is primarily based on the observation of low concentrations of relatively stable EPR active intermediates and small amounts of radical derived products. Since the question still remains to be answered, a detailed analysis is required for the SET processes and the fate of the radical anions, which are the immediate products of the SET.

With the use of a series of newly developed fragmentation probes[11,12] which give both qualitative and quantitative information concerning ketyl formation and decay it is concluded that reactions which involve a small amount of ketyl fragmentation, *i.e.*, the reactions of borohydrides and aluminates, represent minor pathways in their reactions with aromatic ketones or aliphatic halides.[13] Only in the case of very hindered ketones or very good electron acceptors do the reactions of these reducing agents predominantly follow the homolytic pathway (also see Chapter 3 and 5).[13] It has been established that the rate of ketyl fragmentation of probes with the structure *i*, is relatively independent of substitution at R.[11, 12]



i

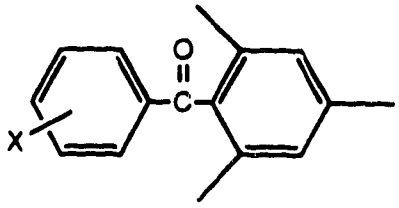
Competitive reactions of the ketyl intermediate at the carbonyl and fragmentation reactions of x^- (x = halogen) can be used to estimate rate

constants for the reactions at the carbonyl since the ketyl fragmentation rate constants k_{fx} are known.[12]

To overcome difficulties arising from the short lifetime of the radical intermediates of the Grignard reactions, which proceed via a SET pathway, but are blind to the EPR spectroscopic method,[5] we use sterically hindered aromatic ketones, **Ia-e**, for the investigation of the Grignard reactions. The Grignard reagents are complex mixtures whose composition is governed by the Schlenk equilibrium (eq 1). The components of the equilibrium are complexed with ether and may have a monomeric, dimeric or polymeric composition.

$$2RMgX \rightleftharpoons RMgX\bullet\ RMgX \rightleftharpoons R_2Mg\bullet\ MgX2 \rightleftharpoons R_2Mg + MgX_2 \qquad (1)$$

However, it was shown by Maruyama[14] that Grignard reagents are mostly monomeric in THF. THF is therefore used as a solvent in this work. For the purpose of this study the reagent is considered to react as RMgX.



Ia: X = 4-Br

b: X = 2-Br

c: X = 3-Br

d: X = H

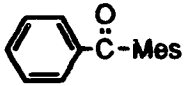
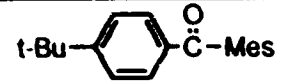
e: X = 4-Cl

Results and Discussion

In this chapter the work is still incomplete and only preliminary results can be reported. Most of the reactions were carried out using *t*-butylmagnesium chloride and 5-hexenylmagnesium bromide. Reactions carried out with butyl-, methyl-, phenyl-, and allylmagnesium chlorides were only screened in order to determine whether 1,2-addition, dehalogenation, 1,4- or 1,6-alkylation or ketyl formation has taken place. Only in the reactions of allylmagnesium chloride with **Ia** or **Ib** were 1,2-addition products detected.

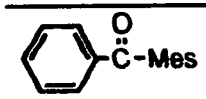
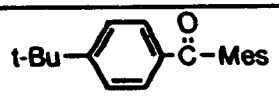
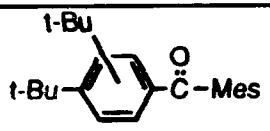
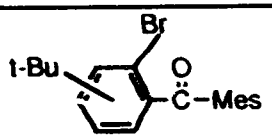
The Cleavage of C-Br Bond Leads to the Formation of 2,4,6-Trimethylbenzophenone (mesityl phenyl ketone, MPK) - The production of MPK and further substitution reactions on the phenyl ring of MPK were observed in the reactions of **Ia, Ib,** and **Ic** with RMgCl (R=*t*-Bu, Bu, Me, Ph), see Scheme VI-3 and Table VI-1, 2, 3, 4, 5.

Table VI-1. Product Distributions in the Reactions of **Ia** and **Id** with *t*-Butylmagnesium Chloride in THF (23 °C).

[RMgCl] /[I]	condition Time (min x 10)	yield, % 		S.M.
1.0(**Ia**)[a]	5	0.0	52.8±3.7	46.4±3.5
2.0(**Ia**)[a]	5	0.0	88.9±2.8	9.4±1.4
16.5(**Ia**) [b]	0.9	0.2 ±0.1	97.5 ±3.9	2.3±0.4
	17.2	0.7±0.2	96.9±4.1	2.4±0.6
1.0(**Id**)[c]	5	NA	43.9±2.7	60.7.±3.8
2.0(**Id**)[c]	0.9	NA	79.7±4.0	22.3±1.3
15.8(**Id**)[d]	0.9	NA	90.1±3.1	8.8±1.1
	17.2	NA	91.7±4.5	8.3±1.4

[a] **[Ia]** = 0.050 M. [b] **[Ia]** = 0.030 M. [c] **[Id]** = 0.051 M. [d] **[Id]** = 0.031 M.

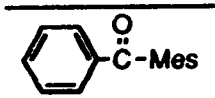
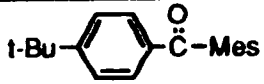
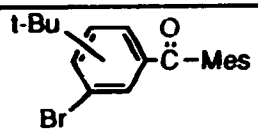
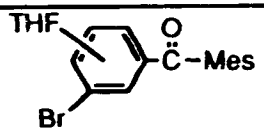
Table VI-2. Product Distributions in the Reactions of **Ib** with *t*-Butylmagnesium Chloride in THF(23 °C).

[RMgCl]/ [Ib]	condition Time(min x10)	yield, %				
				 (e)	 (e)	S.M.
18.3[a]	0.9	19.6±0.9	37.8±2.1		28.1±1.3	12.2±1.9
4.26[b]	6.0	7.3±0.3	48.1±2.8	9.0±0.4	26.3±1.5	9.3±0.9
0.85[c]	22.5	7.3±0.4	0.2±0.1		1.5±1.0	91.6±1.5
14.2[d]	120	15.5±0.7	62.4±3.6	1.4±0.2	10.9 ±1.1	5.7±0.6

[a] [Ib] = 0.030 M. [b] [Ib] = 0.055 M. [c] [Ib] = 0.15 M. [d] [Ib] = 0.027 M. 0.9% (2-tetrahydrofuranyl)-2',4',6'-trimethylbenzophenone and 2.0% *t*-butylated (2-tetrahydrofuranyl)-2',4',6'-trimethylbenzophenone were detected.

[e] The structures of these alkylated products were tentatively assigned on the basis of their GC/IR and GC/MS spectra.

Table VI-3. Product Distributions in the Reactions of **Ic** with *t*-Butylmagnesium Chloride in THF(23 °C).

[RMgCl]/ [Ic]	condition	yield, %				
	Time (min x10)			 (e)	 (e)	S.M.
18.3[a]	0.9	1.4±0.2	4.8±0.3			92.6±2.9
20[b, c]	1008	11.6±1.8	23.8±1.6	trace	trace	53.2±2.3
7.1[d]	504	2.1±0.4	2.0±0.5	1.3±0.2	0.7±0.2	93.8±3.3

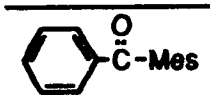
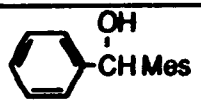
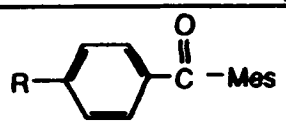
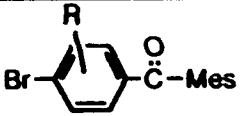
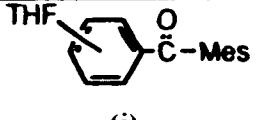
[a] [Ic] = 0.030 M. [b] [Ic] = 0.075 M.

[c] Trace of 4-*t*-butyl-2',4',6'-trimethylbenzhydrol was observed

[d] [Ic] = 0.062 M

[e] The structures of these alkylated products were tentatively assigned on the basis of their GC/IR and GC/MS spectra.

Table VI-4. Product Distributions in the Reactions of **Ia** and **Id** with Grignard Reagents (RMgCl, R = CH_3, Bu, and Ph) in THF (23 °C).[a]

ketone	R	Yield, %					
				 (j)	 (j)	 (j)	SM
Ia [b]	CH_3	10.7±1.2	0.0	2.0±0.5	1.4±0.1	0.9±0.2	82.9±4.0
Id [c]		NA	7.4±0.5	2.4±0.3	NA	0.0	78.1±3.3
Id [d]		NA	17.2±1.5	5.4±0.1	NA	0.0	62.4±2.4
Ia [e]	Bu	12.7±1.7	1.0±0.2	23.7±3.1	14.9±1.8	6.0±0.4	32.7±1.9
Id [f]		NA	10.9±1.6	69.7±2.9	NA	0.0	7.2±0.8
Ia [g]	Ph	5.4±0.8	1.4±0.3	9.0±0.5	0.0	2.3±0.1	81.9±3.1
Id [h]		NA	17.4±2.6	i	NA	8.9±0.6	70.2±2.1

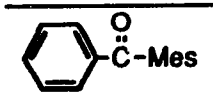
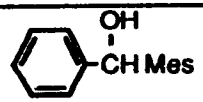
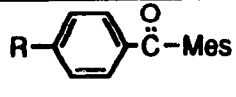
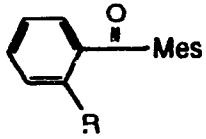
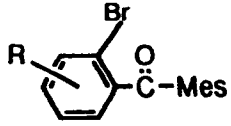
See Footnotes Page 201

Continued.....

Table VI-4. (Continued)

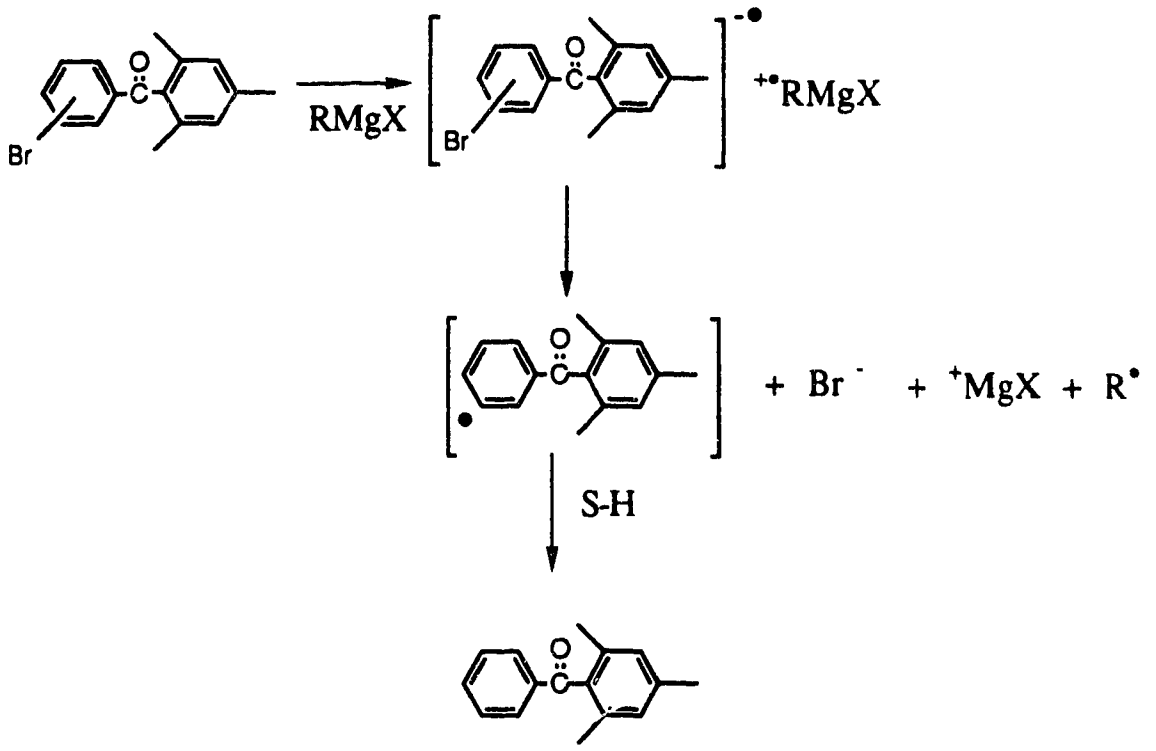
[a] All the reactions were carried out for 12 h. [b] [**Ia**] = 0.044 M; [RMgCl] = 0.15 M. [c] [**Id**] = 0.044 M; [RMgCl] = 0.15M. 7.0% 2-methyl-2',4',6'-trimethylbenzophenone was identified. [d] [**Id**] = 0.246 M; [RMgCl] = 2.50 M. 17.6±0.7% 2-methyl-2',4',6'-trimethylbenzophenone was identified. [e] [**Ia**] = 0.035 M; [RMgCl] = 0.12M. 1.2% (2-tetrahydrofuranyl)-**Ia** was obtained. [f] [**Id**] = 0.035 M; [RMgCl] = 0.12 M. 12.8% 2-butyl-2',4',6'-trimethylbenzophenone was obtained. [g] [**Ia**] = 0.035 M; [RMgCl] = 0.12 M. [h] [**Id**] = 0.035 M; [RMgCl] = 0.12 M. [i] 3.9% 2-phenyl-2',4',6'-trimethylbenzophenone was observed. [j] The structures of these alkylated products were tentatively assigned on the basis of their GC/IR and GC/MS spectra.

Table VI-5. Product Distributions in the Reactions of **Ib** with Grignard Reagents (RMgCl, R = CH_3, Bu, and Ph) in THF (23 °C).[a]

ketone	R	Yield, %					
				 (e)	 (e)	 (e)	SM
Ib [b]	CH_3	52.5±3.1	0.0	0.0	46.8±3.0	0.0	0.5±0.2
Ib [c]	Bu	4.6±0.6	5.3±0.3	34.4±1.9	11.8±0.7	7.1±0.9	0.0
Ib [d]	Ph	29.7±1.5	1.1±0.1	0.0	68.6±3.8	0.0	0.6±0.3

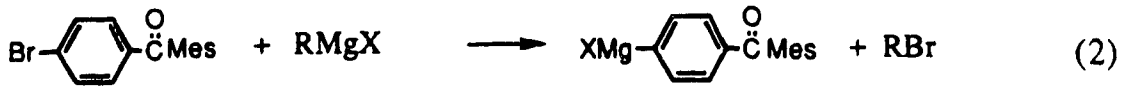
[a] All the reactions were carried out for 12 h. [b] [**Ib**] = 0.092 M; [RMgCl] = 0.75 M. [c] [**Ib**] = 0.083 M; [RMgCl] = 0.25 M. 11.0 % 2-bromo-2',4',6'-trimethylbenzhydrol , and 21.1% dibutyl-2',4',6'-trimethylbenzophenone were obtained.

[d] [**Ib**] = 0.092 M; [RMgCl] = 0.50 M. ~0.5% (2-tetrahydrofuranyl)-2',4',6'-trimethylbenzophenone and ~ 0.3% diphenyl-2',4',6'-trimethylbenzophenone were observed. [e] The structures of these alkylated products were tentatively assigned on the basis of their GC/IR and GC/MS spectra.



Scheme VI-3

Since MPK is formed during the reactions of **Ia** , **Ic** and **Ib** with *t*-butylmagnesium chloride, it appears that fragmentation of the substrate ketyls competes favorably with alkylation. When the reaction mixture was quenched with D_2O there was no deuterium incorporation into the carbon-bromine bond fragmentation product MPK. The absence of deuterium incorporation excludes the possibility that halogen exchange between the aromatic bromides and the alkylmagnesium halides (eq 2) can take place.

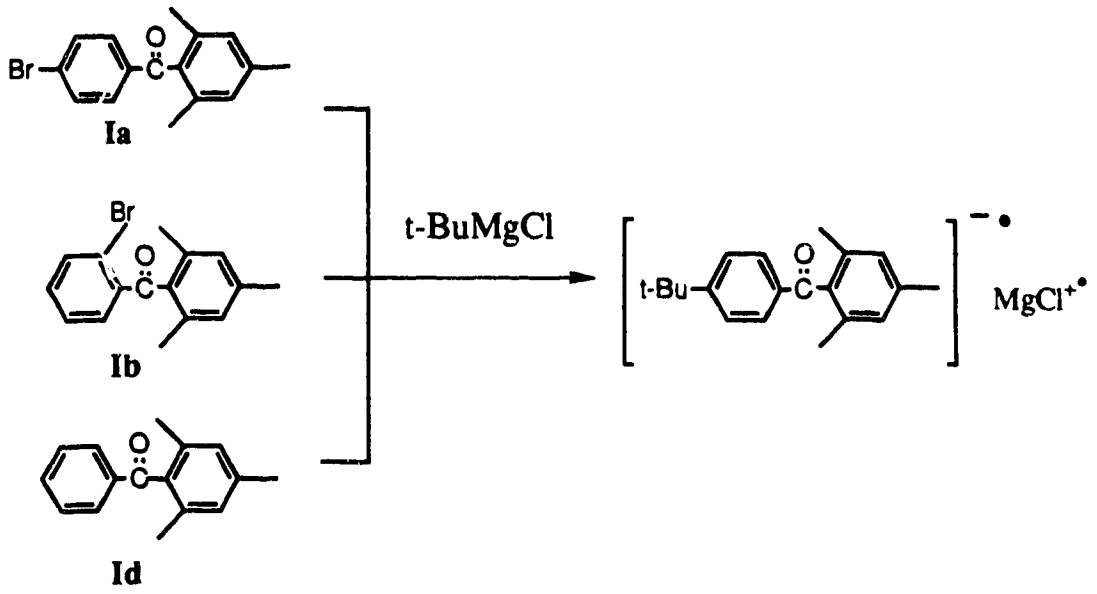


(2)

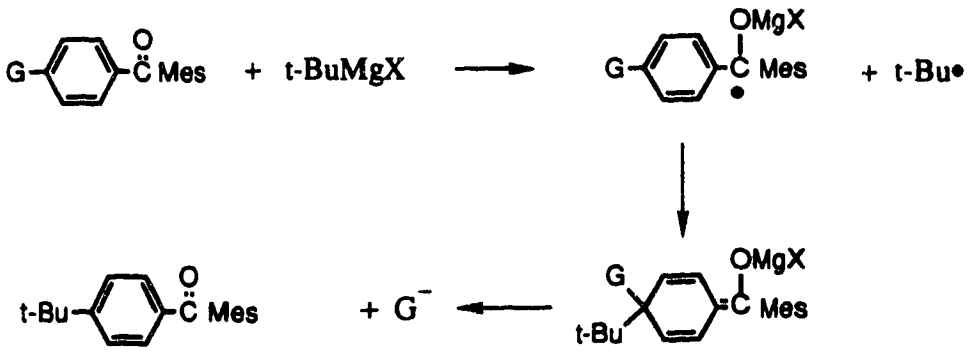
The Reactions of Ia, Ib, and Id with *t*-Butylmagnesium Chloride - The formation of a common product, 4-*t*-butyl-2',4',6'-trimethylbenzophenone (see Table VI-1-2), from the reactions of the three substrates, **Ia, Ib,** and **Id**, with *t*-butylmagnesium chloride suggests that the same intermediate, MPK, leads to the formation of 4-*t*-butyl-2',4',6'-trimethylbenzophenone, see Scheme VI-3 and Scheme VI-5. The production of 4-*t*-butyl-2',4',6'-trimethylbenzophenone does not depend on air-oxidation, since its ketyl is observed spectroscopically (EPR) in a sealed tube before the reaction is quenched.

Okubo in 1977 reported that 4'-methoxy and 4'-cyano substituents on 2,3,5,6-tetramethylbenzophenone were effectively replaced by benzyl- and *t*-butylmagnesium chloride via a S_{RN}-type mechanism, and that both the ketyl radicals of the starting materials and the ketyl radicals of the products were observed spectroscopically.[16]

Since 4-*t*-butyl-2',4',6'-trimethylbenzophenone is produced during the reaction of *t*-butylmagnesium chloride with **Ia, Ib,** and **Id** (Scheme VI-4) the substitution is not the result of *ipso* addition followed by elimination of the bromide anion (eq 3) as was previously suggested[16].



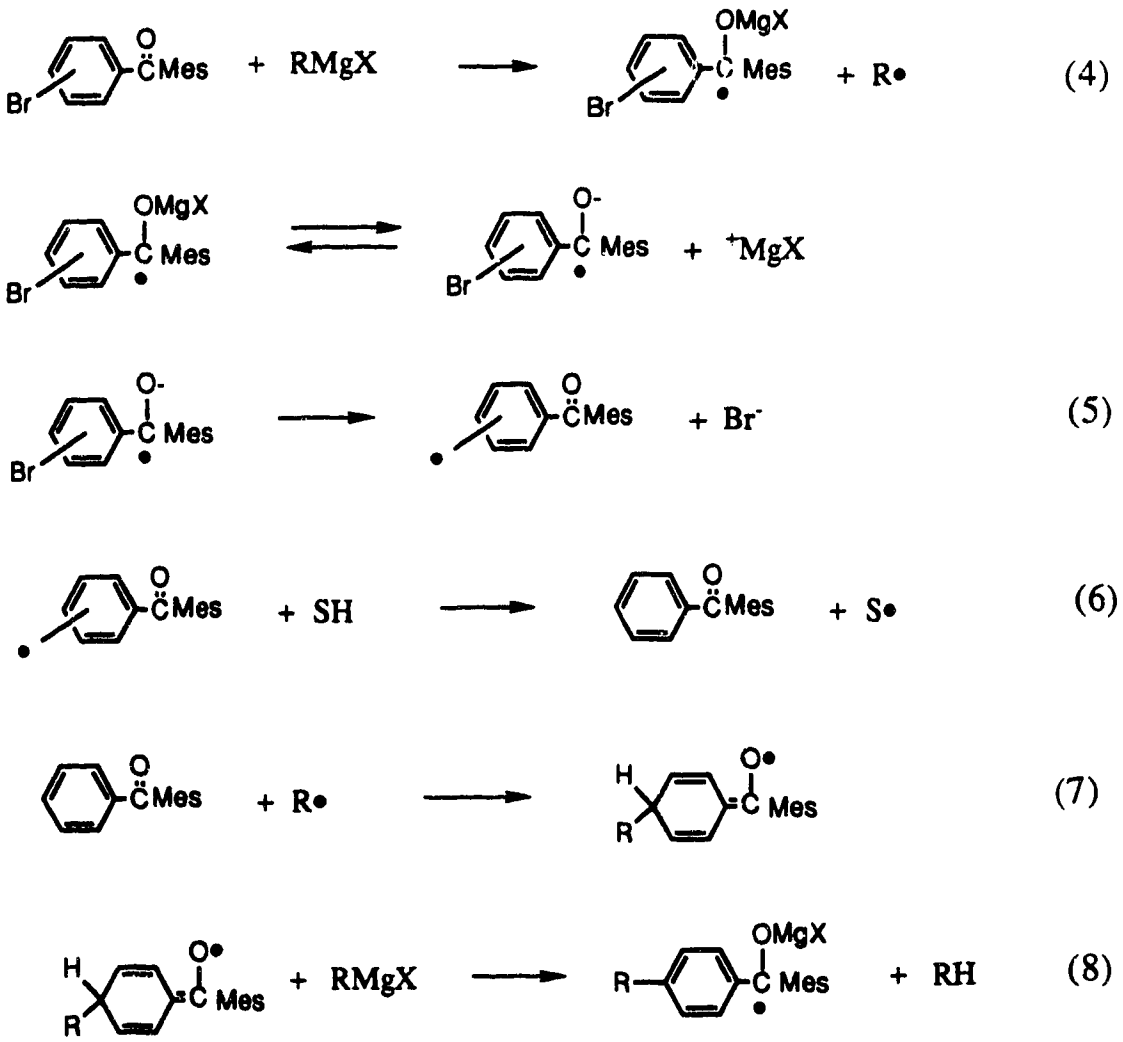
Scheme VI-4



(3)

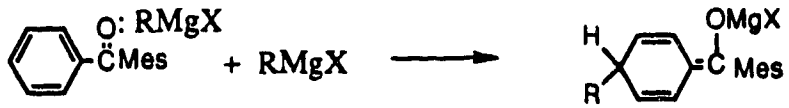
When *t*-butylmagnesium chloride (0.05 M) was allowed to react with 4-bromo-2',4',6'-trimethylbenzophenone (**Ia**, 0.05 M) the reaction produced a 50% yield of only one product 4-*t*-butyl-2',4',6'-trimethylbenzophenone. When the concentration of *t*-butylmagnesium chloride was doubled (0.10 M) the yield was approximately doubled (see Table VI-1). The stoichiometry of the reaction (~2:1) suggests that the

products are formed by a radical mechanism which uses two moles of the Grignard reagent for each mole of the ketone that reacts. Since MPK is produced as an intermediate in the formation of the substitution product a dehalogenation followed by substitution can be proposed (see Scheme VI-5). Subsequent oxidation of the ketyl with molecular oxygen yields stable reaction products when the reaction is quenched.



Scheme VI-5

A less attractive, but possible, alternative to reaction 7, (eq 7a), is the attack of the Grignard reagent on the complex of MPK to give the anion, ii (eq 7a).



(7a)

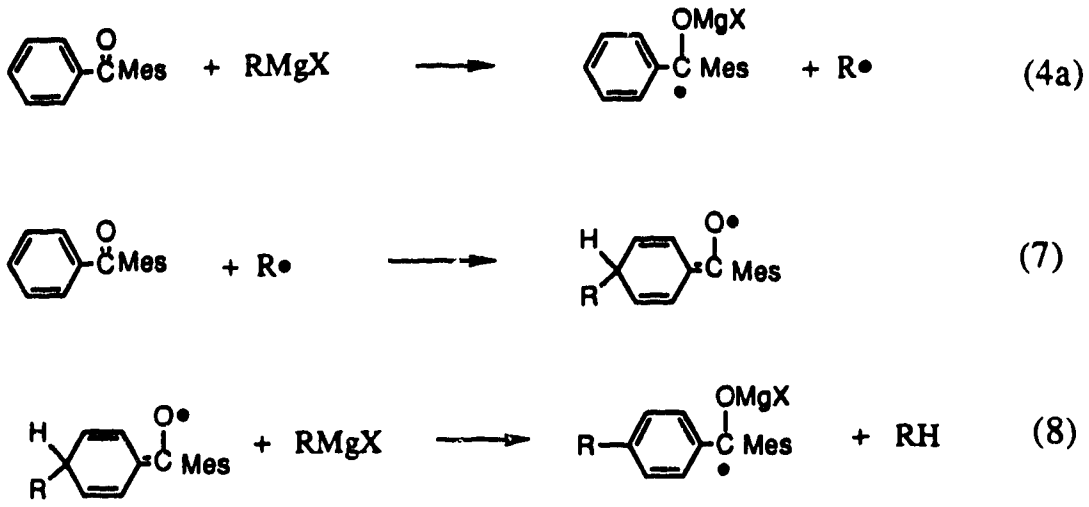
(ii)

(8a)

The subsequent reaction of (ii) with the alkyl radical will yield the same intermediate ketyl (eq 8a).

The substitution mechanism which requires at least two moles of the Grignard reagent, Scheme VI-5, assumes that MPK is the first major neutral, nonradical intermediate that is formed. The reaction of MPK with *t*-butylmagnesium chloride was carried out using 1:1 and 2:1 molar ratios of the Grignard reagent to ketone, see Table VI-1. Within experimental error the same stoichiometry was observed. The reaction products are consistent with the proposed mechanism, Scheme VI-5, but does not involve ketyl fragmentation (Scheme VI-6).

Both reaction sequences in Scheme VI-5 and VI-6 contain reactions which involve the intermediacy of a ketyl (or magnesium complexed ketyl), reactions 4, 4a, and 8. The EPR spectra of the reaction mixtures were recorded.



Scheme VI-6

The Reaction of Ic with *t*-Butylmagnesium Chloride - The reaction of **Ic** appeared to be much slower than that of either **Ia** or **Ib**. The reaction was quenched after a short period of time and the major product aside from MPK was also 4-*t*-butyl-2',4',6'-trimethylbenzophenone, see Table VI-3.

Two radical derived products, although only formed in trace amounts, the alcohol, 4-*t*-butyl-2',4',6'-trimethylbenzhydrol, and the combination product from the solvent radical (THF•) and the aromatic radical, tetrahydrofuranyl-**Ic**, were also obtained in this slow reaction. Presumably these products are formed as by-products since the radical concentrations become higher in the slower reaction.

Since ketyl fragmentation for *meta*-substituted benzophenone is 10^2 times slower than the fragmentation rate of a *para*-substituted one,[12] alkylation competes more favorably and a small amount of substituted starting material is also produced (see Table VI-3).

EPR Spectroscopic Observation of Aryl Mesityl Ketyl - The proposed mechanism (Scheme 5 or 6) predicts that the final product of the reaction of two moles of RMgX with substituted or unsubstituted MPK is the alkylated aromatic ketyl. As predicted the reaction of **Ia, Ib** or **Id** with *t*-butylmagnesium chloride or 5-hexenylmagnesium bromide with **Id** quickly gave the EPR spectrum of MPK. The spectrum gradually change to that of the adduct radical anion of the alkylated MPK.

To slow down ketyl fragmentation and increase the possibility of observing radical cyclization, 4-chloro-2',4',6'-trimethylbenzophenone (**Ie**) was allowed to react with 5-hexenylmagnesium bromide. The ketyl radical anion was immediately formed, however, the spectrum of MPK was not observed but only the spectrum presumed to be that of the alkylated ketyl of the starting material was observed.

The mechanisms (Schemes VI-5 or VI-6) further predict that, since the reaction (1:2, ketone:Grignard reagent) yields a stable ketyl, one mole of ketyl should be formed for each mole of starting ketone that undergoes reaction.

Although the product ketyl was formed and was, with the exception of the reactions of *t*-butylmagnesium chloride, indefinitely stable the yield of ketyl varied (1-91%) with the Grignard reagents used, *i.e.*, when a 2:1 mole ratio of a Grignard reagent to a ketone was allowed to react, see Table VI-6.

The Reactions of Id and Ie With 5-Hexenylmagnesium Bromide - In order to observe the cyclization of the incipient radical

Table VI-6. The Yields of Ketyls (EPR) Formed from the Reactions of Grignard Reagents with Ketones (2:1) in THF.[a].

RMgX	Ketone	Ketyl yield, % (time)
PhMgCl	**Id**	81 (23 h)
MeMgCl	**Id**	92 (24 h)
MeMgCl	**Ia**	1 (1 h)
5-Hexenylmagnesium bromide	**Id**	91 (24 h)
5-Hexenylmagnesium bromide	**Ie**	23 (1 h)[b]
t-BuMgCl	**Id**	1 (0.5 h)
t-BuMgCl	**Ia**	5 (5 h)
PhMgCl	**Ia**	30 (18 h)

[a] The yields of the ketyls were determined when the intensities of the EPR signals reached to their maximum.

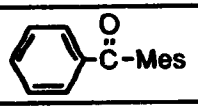
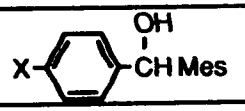
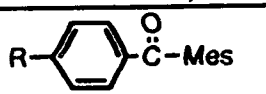
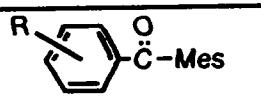
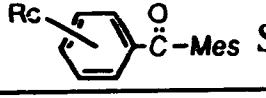
[b] It was determined before the maximum yield of the ketyl was reached.

produced from the Grignard reagent a probe which fragments more slowly than the bromodiaryl ketone was used. When 5-hexenylmagnesium bromide was allowed to react with 4-chloro-2',4',6'-trimethylbenzophenone, **Ie**, only one alkylated product (92.3%), 4-(5-hexenyl)-2',4',6'-trimethylbenzophenone (**Ie**), was formed along with a small amount of reduction product (5.4%), 4-chloro-2',4',6'-trimethylbenzhydrol. When the Grignard reagent was allowed to react with **Id**, four products were obtained along with 34% MPK recovery. The products are 21.5% 2,4,6-trimethylbenzhydrol and three alkylated derivatives of MPK (see Table VI-7).

The IR spectra of two of the three alkylated derivatives of MPK showed absorption peaks (3072 cm^{-1}, C=C-**H**) diagnostic of the 5-hexenyl substituted products. The major isomer (28.1%) was isolated and its ^1H NMR spectrum allowed its structure to be assigned as 4-(5-hexenyl)-2',4',6'-trimethylbenzophenone. The IR spectrum of one of the minor isomers (8.3%) not only showed absorption peaks (3072 cm^{-1}, C=C-**H**) diagnostic of the 5-hexenyl substituted products but also showed absorption peaks (1606 and 1575 cm^{-1}) diagnostic of *ortho*-substituted phenyl mesityl ketone, it can be therefore tentatively assigned as the 2-(5-hexenyl)-2',4',6'-trimethylbenzophenone. The third isomer (7.7%) can be tentatively assigned as the cyclized addition product, since the IR absorption at 3080-3070 cm^{-1} was absent (no olefinic hydrogen). Since the Grignard reagent when formed is a mixture which contains ~ 9% of cyclopentylmethylmagnesium bromide, the production of a 7.7% yield of cyclopentylmethyl substitution is expected.

The lack of a large amount of the rearranged substitution product confirms the assumption[10] that the reaction of the radical with the ketyl is extremely fast, *i.e.*, faster than the rearrangement of 5-hexenyl radical.

Table VI-7. Product Distributions in the Reactions of **Id** and **Ie** with Grignard Reagents 5-Hexenylmagnesium Bromide in THF (23 °C).[a]

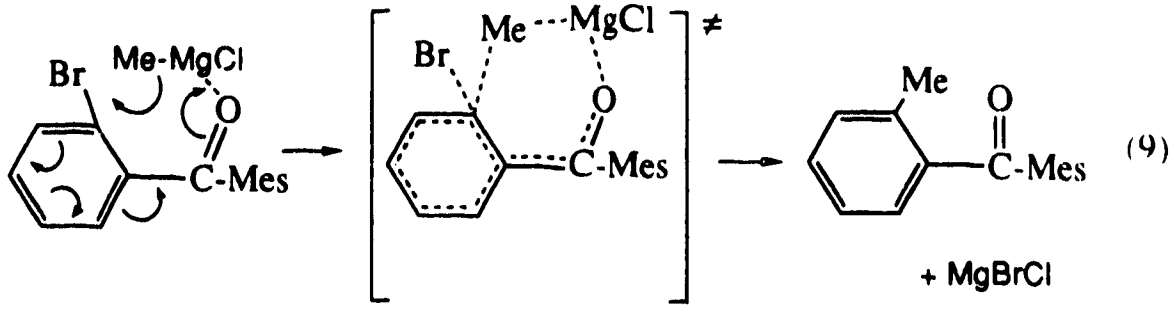
ketone	Yield, %					
						SM
Ie [a]	0.0	5.4±0.7 (X=Cl)	92.3±3.2 (R=5-hexenyl)	0.0	0.0	0.5±0.2
Id [b]	NA	21.5±1.4 (X=H)	28.1±2.1 (R=5-hexenyl)	8.3±1.1[c]	7.7±1.5[d]	34±2.7

[a] [**Ie**] = 0.050 M; [RMgCl]= 0.10 M. The reaction was carried out for 16 h. A yield of 22% of ketyl was detected by EPR at the beginning and 90% of ketyl was detected after 24 h. [b] [**Id**] = 0.051 M; [RMgCl] = 0.10 M. The reaction was carried out for 24 h. A yield of 91% ketyl was detected after a few h. [c] The structure of the alkylated product was tentatively assigned to 2-(5-hexenyl)-2',4',6'-trimethylbenzophenone on the basis of its GC/IR and GC/MS spectra. [d] The structure of the alkylated product was tentatively assigned to 4-cyclopentylmethyl-2',4',6'-trimethylbenzophenone on the basis of its GC/IR and GC/MS spectra.

The Reactions of Ia with Methylmagnesium Chloride, Butylmagnesium Chloride, and Phenylmagnesium Chloride - The reactions all afforded MPK (yield from 5% to 11%), the product derived from ketyl fragmentation. With butylmagnesium chloride or phenylmagnesium chloride, the reduction product, 2,4,6-trimethylbenzhydrol, was also formed. Benzhydrol has been rationalized as being a product formed from the disproportionation of the ketyl and the radical formed from the Grignard reagent. The benzhydrol produced in the reaction of PhMgCl with **Ia** is no doubt formed by H abstraction by the ketyl from the solvent THF. The reactions of methylmagnesium chloride or butylmagnesium chloride produced 1,4-addition alkylated products as well as 1,6-addition alkylated products. Only the 1,6-addition product was detected from the reaction of phenylmagnesium chloride with **Ia**, see Table VI-4. In no case was a 1,2-adduct detected.

The Reaction of Ib with Methylmagnesium Chloride, Butylmagnesium Chloride, and Phenylmagnesium Chloride - The reactions of MeMgCl with **Ib** gives MPK and 2-methyl-2',4',6'-trimethylbenzophenone as the major products. On the basis of the half wave potentials for the reactants it was argued that the energetics for SET between MeMgX and benzophenone are not favorable.[2b,c] However, these conclusions can only be correct if a complex prior to electron transfer is ignored. Since the formation of MPK in this study is best rationalized by a SET mechanism, the conclusion reached from the redox potentials must be incorrect. The formation of 2-methyl-2',4',6'-trimethylbenzophenone can be formed via either a SET pathway or a polar pathway (eq 9). The nucleophilic substitution of aromatic bromine in 2-bromobenzophenone

with the Grignard reagents (MeMgBr, EtMgBr) was reported by Jongsma and Bickelhaupt(1973)[20]. The reaction of a hindered ketone, **Ib**, facilitates the SET process but does not completely eliminate the displacement reaction. No 1,2-adduct was detected, see Table VI-5.



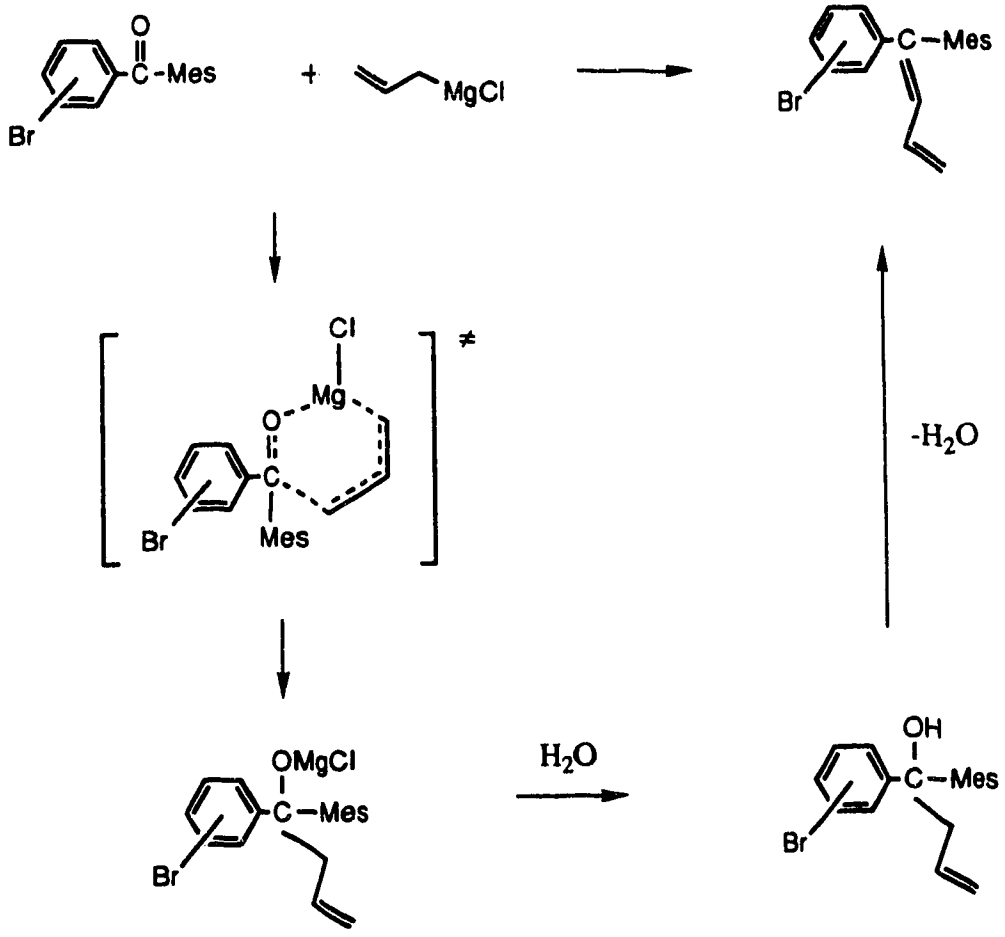
(9)

When the reaction between BuMgCl and **Ib** was carried out, the products could all be rationalized by ketyl-radical pathways. The production of MPK (4.6%) from ketyl fragmentation-hydrogen atom abstraction and the formation of the two carbinols, 2,4,6-trimethylbenzhydrol (5.3%), and 2-bromo-2',4',6'-trimethylbenzhydrol (11.0%) are best explained by a ketyl-hydrogen atom abstraction reaction with the butyl radical (*i.e.*, disproportionation). The alkylated products were produced presumably by the general mechanism given in Scheme VI-5 (see Table VI-5).

In the reaction of **Ib** with PhMgCl, the major products are MPK and the phenylated product, 2-phenyl-2',4',6'-trimethylbenzophenone, see Table VI-5. When THF-d_8 was used as a solvent for the reaction deuterium was incorporated in the MPK and in the phenylated product, 2-phenyl-2',4',6'-trimethylbenzophenone. The deuterium content of the materials has of yet not been quantitatively determined.

Okubo[19] has previously reported that the reaction of MPK with PhMgBr affords 2-phenyl-2',4',6'-trimethylbenzophenone. Neither *para*-phenylated products nor benzpinacol were detected.[19]

Grignard Reactions of Allylmagnesium Bromide Proceed Most Likely via a Concerted Pathway-The criteria (dehalogenation, alkylation, and ketyl formation) used to determine whether a SET reaction is involved in the reactions of aromatic ketones, were also applied to the reactions of allylmagnesium bromide. The reactions of **Ia** or **Id** with excess, or with two fold excess of CH_2=$CHCH_2MgCl$ for 14 h, gave exclusively 1,2-addition products, bromophenylallylmesitylcarbinol. However, since the alcohol bromophenylallylmesitylcarbinol is not stable, and readily dehydrates, only its elimination product 1-bromophenyl-1-mesityl-1,3-butadiene was detected by GC/MS and GC/IR. No dehalogenated products were observed, see Scheme VI-7.


O
C-Mes
Br
+
MgCl
C-Mes
Br
Cl
Mg
O
C
Br
Mes
≠
-H2O
OMgCl
C-Mes
Br
H2O
OH
C-Mes
Br

Scheme VI-7

Experimental

General - The solutions of all oxygen- and water-sensitive Grignard reagents were prepared in a dry box under a dry nitrogen atmosphere with flame dried glassware that were fitted with septa to protect them from moisture. The transfer of solutions before they were degassed was performed with gas tight syringes using standard techniques. The ^1H NMR spectra were obtained using either a Bruker AM-400 (400 MHz), Bruker AM-300 (300 MHz), or Bruker WH-200 (200 MHz) NMR spectrometers. All chemical shift values are reported in δ units relative to Me_4Si (δ = 0.00 ppm) in deuteriochloroform. The EPR spectra were obtained using a Bruker ER 200E/SRC spectrometer fitted with a ER 4102 ST-Universal X-Band Resonator operated at 9.6 GHz. Coupling constants are reported in gauss (G), and the g values were determined using a diphenylpicryhydrazyl (DPPH) external standard.

GC analysis was performed using a HP5840A gas chromatograph equipped with a hydrogen flame ionization detector and a stainless steel column (25ft x 1/4 inch) packed with 10% SE-30 on Chromosorb W (100-200 mesh) and interfaced with a HP5840A integrater.

High-resolution mass spectral data were obtained with a KRATOS MS50 high-resolution EI^+ mass spectrometer (70 ev) connected to a DS 55 data system. The isotopic content of the products was determined using GC/MS in conjunction with ^1H and ^2H NMR. Gas phase chromatograph/mass spectra (GC/MS) were recorded using a VG-70E mass spectrometer interfaced to a 11-250 data system and coupled to a Varian

Vista 6000 GC, which was fitted with a DB-1 capillary column. Gas phase chromatograph/infrared spectra (GC/IR) were obtained using a HP-5965A IRD spectrometer interfaced to a HP5890 gas chromatograph (Hewlett-Packard) fitted with a glass capillary column (Hewlett-Packard ultra 2, 25 m x 0.32 mm x 0.52 μ).

Materials - Tetrahydrofuran (Aldrich, HPLC grade) was dried over KOH for over 7 days and then distilled under Argon from sodium benzophenone ketyl immediately prior to use. **THF-d8** (GIC, 99% D) was purified by the same method. **5-Hexenylmagnesium bromide** was prepared from 6-bromo-1-hexene (ALDRICH), which was purified by vacuum distillation, and all other Grignard reagents were purchased from ALDRICH. All the Grignard reagents were titrated with *sec*-butyl alcohol and 1,10-phenanthroline using the procedure of Watson and Eastham.[22]

The preparations of **Ia-d** have been described previously, see Chapter 3.

4-Chloro-2',4',6'-trimethylbenzophenone (Ie) was prepared by treating a CS_2 solution of corresponding *p*-chlorobenzoyl chlorides with mesitylene in the presence of aluminum trichloride.[25] The products were isolated and purified by recrystallization from pet. ether (35-60 °C)/acetone: mp 68.5-69.5 °C (lit.[26] mp 65-67 °C; lit.[27] mp 67-69 °C,). ^1H NMR(200 MHz, CD_2Cl_2) δ 7.75(m, 2H), 7.45(m, 2H), 6.92(s, 2H), 2.35(s, 3H), 2.08(s, 6H). MS, *m/z*$^+$(rel. intensity) 260(31), 258(92), 243(28), 223(100), 208(31), 147(40), 119(18), and 77(6). HRMS, *m/z*$^+$ 260.0782 (M^+, Cl^{37}), 258.0807 (M^+, Cl^{35}) (Calcd for $C_{16}H_{15}OCl^{37}$:

260.0782; $C_{16}H_{15}OCl^{35}$: 258.0812). Anal. Calcd for $C_{16}H_{15}OCl$: C, 74.27; H, 5.84; Cl, 13.70. Found: C, 74.20; H, 5.89; Cl, 13.82.

General procedure for the Grignard reactions of diaryl ketones and the quantitative GC analysis of the products - All reactions were carried out in dried and degassed Pyrex H tubes.

An aliquot of a solution of RMgX (0.05-1.5 M) in THF was placed in one arm of a Pyrex H tube, an aliquot of a THF solution of the substrate (0.03-0.30 M) containing 1,4-di-*t*-butylbenzene was placed in the other arm of the H tube. The tube was degassed under vacuum (three times) and sealed. The two solutions were thermostated at the desired temperature and mixed. The reaction was carried out for the time specified, see Tables VI-1-5, and VI-7. The reaction tube was cooled, opened, quenched with an ammonium chloride solution and was dried over anhydrous $MgSO_4$. The products were analysed by GC. The area ratios were converted to mole ratios for quantitative determinations by using standard calibration curves constructed from known mixtures of the authentic materials. Products were identified by a comparison of their retention times, GC/MS, GC/IR spectra, with those of authentic materials except for compounds which are noted in Tables VI-1-5, and VI-7, these structures are only tentatively assigned on the basis of their GC/MS and GC/IR spectra. The quantitative results listed in Tables VI-1-5, and VI-7 are the average results of two or more independent experiments. When necessary, separations were made by preparative TLC and the products were subjected to NMR analysis.

EPR spectroscopy of the reaction mixtures from *t*-butylmagnesium chloride or 5-hexenylmagnesium bromide and the substrates: 4-bromo-2',4',6'-trimethylbenzophenone (Ia), 2-

bromo-2',4',6'-trimethylbenzophenone (Ib), 2',4',6'-trimethylbenzophenone(Id), and 4-chloro-2',4',6'-trimethylbenzophenone (Ie) - A THF solution of the substrate (0.05 M) was placed in one of the divided arms of a H tube fitted with a quartz EPR tube. A second THF solution of RMgX (2.0 mL, 0.05-0.10 M) was placed in the second arm of the H tube and the reaction vessel was degassed three times, and then sealed. The solutions were mixed at room temperature and the filled EPR tube was immediately placed into the cavity of the EPR spectrometer and its spectra were recorded periodically.

When a THF solution of 2,4,6-trimethylbenzophenone (MPK, 0.05M) was mixed with a THF solution of *t*-butylmagnesium chloride (0.10M), the ketyl radical anion of MPK was initially observed within a few minutes, and the solution is wine-reddish in color within 30 minutes. The spectrum contains 90 lines with a = 0.236 G. The hyperfine splitting constants (hfsc) and the splitting patterns of the radical anion was the same as the spectrum reported previously, for the ketyl of MPK[6c] The spectrum changed gradually. After > 1 hour, only the ketyl radical anion of 4-*t*-butyl-2',4',6'-trimethylbenzophenone was observed. Its spectrum, containing three broad lines, is identical to the spectrum of the ketyl previously reported.[15] The ketyl is stable for several days (g_x = 2.00239, a = 4.875G). The EPR spectrum obtained from the reaction of **Ia** with *t*-butylmagnesium chloride is identical to that obtained from the reaction of **Ib** with *t*-butylmagnesium chloride after a few hours.

Ketyl yields of over 90% were obtained from the reactions of 5-hexenylmagnesium bromide with **Id.**

Calibration of Ketyl Radical Anion Concentration in THF using DPPH - After the overmodulated EPR signal of a Grignard reaction mixture in THF was recorded, the overmodulated signal of a THF solution of 2,2-diphenyl-1-picrylhydrazylhydrate (DPPH) free radical (0.0050M) was recorded at exactly the same instrumental conditions. The ketyl radical anion concentration was calculated according to the method given in Appendix I [28](Table VI-6).

4-*t*-Butyl-2',4',6'-trimethylbenzophenone: bp 179-181 °C/4mmHg (lit.[23] bp 163 °C/0.3mmHg); ^{1}H NMR(300 MHz, CD_2Cl_2) δ 7.75-7.45(dd, AA'BB', J=8.5 Hz, 4H), 6.90(s, 2H), 2.35(s, 3H), 2.10(s, 6H), 1.35(s, 9H); APT ^{13}C NMR(CD_2Cl_2) δ 200.16(+), 157.13(+), 138.09(+), 137.06(+), 134.67(+), 133.99(+), 129.25(-), 128.21(-), 125.58(-), 34.99(+), 30.93(-), 20.99(-), 19.02(-); IR(gas phase) ν 2970vs, 2879w, 1683vs(C=O), 1607s, 1477w, 1405w, 1266vs, 1175m, 1102w, 1017w, 912s, 848s, 775w, and 706w cm^{-1}. MS, *m/z*$^+$ 280(M$^+$, 26), 265(11), 223(100), 208(18), 161(10), 147(26), 119(25), 91(18), and 57(8).

***t*-Butylated 2-Bromo-2',4',6'-trimethylbenzophenone** was obtained from the reaction of **Ib** with *t*-BuMgCl: IR(gas phase) ν 2972vs, 1692s (C=O), 1680s, 1596, 1476m, 1383m, 1279s, 1108m, 1045m, 912s, 848s, 765w, and 697w cm^{-1}. MS, m/z$^+$ 360 (M$^+$, Br^{81}), 358 (M$^+$, Br^{81}), 303, 301, 279, 223, 208, 147, 119, 103, 91, 77, and 57.

(2-Tetrahydrofuranylated) 2',4',6'-trimethylbenzophenone was obtained from the reactions of **Ia** with MeMgCl, BuMgCl, and PhMgCl: IR(gas phase) ν 2981s, 2955s, 2874s, 1884(C=O)vs, 1608s,

1415w, 1347w, 1283vs, 1172m, 1073vs, 910s, 848s, and 763w cm^{-1}; MS, *m/z*$^+$ 294(M^+), 249, 223, 208, 147, 119, 105, 91, and 71.

(2-Tetrahydrofuranylated) 4-*t*-Butyl-2',4',6'-trimethylbenzophenone was obtained from the reaction of **Ib** with *t*-BuMgCl: IR(gas phase) ν 2970, 1674(C=O), 1604, 1570, 1420, 1253, 1062, 970, 905, and 840 cm^{-1}. MS, *m/z*$^+$ 350 (M^+), 335, 307, 293, 279, 265, 247, 237, 223, 207, 187, 147, 133, 120, 105, 91, 77, and 57.

Two **isomers of Di-*t*-Butyl-2',4',6'-trimethylbenzophenone** was obtained from the reaction of **Ib** with *t*-BuMgCl: **Di-*t*-Butyl-2',4',6'-trimethylbenzophenone isomer a** : IR(gas phase) ν 2969, 1679 (C=O), 1603, 1479, 1396, 1235, 1176, 1114, 917, and 847 cm^{-1}. MS, *m/z*$^+$ 336 (M^+), 321, 303, 279, 261, 223, 147, 119, 91, 71, and 57. **Di-*t*-Butyl-2',4',6'-trimethylbenzophenone isomer b**: IR(gas phase) ν 2969, 2880,1658 (C=O), 1568, 1477, 1370, 1254, 1169, 1106, 1037, 975, 910, and 847 cm^{-1}. MS, *m/z*$^+$ 336 (M^+), 321, 298, 281, 261, 241, 223, 208, 161, 147, 121, 105 91, 57, and 41.

***t*-Butylated 3-Bromo-2',4',6'-trimethylbenzophenone** was obtained from the reaction of **Ic** with *t*-BuMgCl: MS, *m/z*$^+$360 (M^+, Br^{79},45), 358 (M^+, Br^{81}, 47), 303 (98), 301 (100), 279 (72), 223 (65), 147 (100), 119 (68), 91 (35), and 57 (50).

(2-Tetrahydrofuranylated) 4-Bromo-2',4',6'-trimethylbenzophenone was obtained from the reaction of **Ia** with *t*-BuMgCl: IR(gas phase) ν 2931, 2900, 1679(C=O), 1554, 1245, 1065, and 905 cm^{-1}. MS, *m/z*$^+$ 374(M^+), 372, 359, 357, 331, 329, 303, 301, 222, 206, 173, 147, 133, 120, 105, and 91.

(2-Tetrahydrofuranylated) 3-Bromo-2',4',6'-trimethylbenzophenone was obtained from the reaction of **Ic** with *t*-BuMgCl: IR(gas phase) ν 2975, 1687 (C=O), 1591, 1372, 1245, 1175, 1110, 924, and 848 cm^{-1}. MS, *m/z*$^+$ 374 (M^+, Br^{81}, 47), 372 (M^+, Br^{79}, 42), 329 (30), 303 (91), 293 (95) , 222 (28), 147 (100), 119 (50), and 91 (35).

4-(5-Hexenyl)-2',4',6'-trimethylbenzophenone was obtained from the reaction of 5-hexenylmagnesium bromide with **Ie** or **Id** and isolated by preparative TLC on silica gel (pre-coated TLC plates 60F-254, 5/95 Et_2O/Benzene as the eluant) : ^1H NMR(200 MHz, $CDCl_3$) δ 7.60(d, 2H), 7.11(d, 2H), 6.55(s, 2H), 5.65(m, 1H), 4.90(m, 1H), 4.82(dm, 1H), 2.54(t, 2H), 2.18(s, 3H), 1.96(s, 6H), 1.50(m, 2H), 1.85(m, 4H); MS, *m/z*$^+$ (relative intensity) 306(M^+, 16), 223(100), 208(10), 147(15), 119(11), 91(9), and 77(4); HRMS, *m/z*$^+$ obsd 306.1980 (M^+, calcd for $C_{22}H_{26}O$: 306.1984); IR(gas phase) ν 3072 (nonconjugated C=C-H), 3021, 2936, 2870, 1683(C=O), 1606 (*para*-substituted phenyl mesityl ketone), 1445, 1264, 1171, 910, and 848 cm^{-1}.

Two other isomeric products with the formula $C_{22}H_{26}O$, that were obtained from the reaction of **Id** with 5-hexenylmagnesium bromide, were isolated as a mixture by preparative TLC:

a (tentatively assigned to **2-(5-hexenyl)-2',4',6'-trimethylbenzophenone**): IR(gas phase) ν 3072(nonconjugated C=C-H), 3016, 2933, 2870, 1678(C=O), 1606, 1575 (*ortho*-substituted phenyl mesityl ketone), 1446, 1248, 1173, 910, 849, 746, and 613 cm^{-1}; MS, *m/z*$^+$ 306(M^+, 8), 229(60), 223(100), 208(12), 147(20), 119(16), and 91(15).

b (tentatively assigned to **4-(cyclopentylmethyl)-2',4',6'-trimethylbenzophenone**): IR(gas phase) ν 3025w, 2958, 2878,

1683(C=O), 1606 (*para*-substituted phenyl mesityl ketone), 1440, 1264, 1171, 909, and 848 cm^{-1}; MS, *m/z*+ 306(M^+, 7), 223(100), 147(15), 119(11), and 91(6).

2-Metyl-2',4',6'-trimethylbenzophenone was obtained from the reactions of either **Ib** or **Id** with MeMgCl: IR(gas phase) ν 3022, 2935, 1681(C=O), 1608, 1580(*ortho*-substituted phenyl mesityl ketone), 1457, 1387, 1300, 1249, 1175, 950, 908, 849, and 735 cm^{-1}. MS, *m/z*+ 238(M^+, 17), 237(11), 224(18), 223(100), 208(16), 147(25), 119(17), and 91(25).

4-Metyl-2',4',6'-trimethylbenzophenone was obtained from the reactions of either **Ia** or **Id** with MeMgCl: IR(gas phase) ν 3031, 2933, 1684(C=O), 1608(*para*-substituted phenyl mesityl ketone), 1434, 1266, 1172, 909, 847, and 750 cm^{-1}. MS, *m/z*+ 238(M^+), 223, 208, 179, 147, 119, and 91.

Methylated 4-Bromo-2',4',6'-trimethylbenzophenone was obtained from the reactions of either **Ia** with MeMgCl: IR(gas phase) ν 3020, 2934, 1682(C=O), 1585, 1444, 1386, 1246, 1200, 1090, 960, 910, and 851 cm^{-1}. MS, *m/z*+ 318 (M^+, Br^{81}), 316 (M^+, Br^{79}), 303, 301, 286, 237, 222, 197, 178, 147, 119, 91, and 77.

2-Phenyl-2',4',6'-trimethylbenzophenone[19] was obtained from the reaction of either **Ib** or **Id** with PhMgCl: IR(gas phase) ν 3067, 2935, 1674(C=O), 1608, 1572(*ortho*-substituted phenyl mesityl ketone), 1442, 1276, 1177, 909, 849, 760, and 699 cm^{-1}. MS, *m/z*+ 300(M^+), 300, 285, 267, 223, 181, 153, 152, 147, 119, 91, 77, 65, and 41.

Phenyl-2',4',6'-trimethylbenzophenone (a structural isomer of 2-Phenyl-2',4',6'-trimethylbenzophenone) was obtained from the reaction of **Ia** with PhMgCl: IR(gas phase) ν 3040, 2933, 1684(C=O),

1605, 1447, 1263, 1173, 1008, 965, 910, 849, and 748 cm^{-1}. MS, *m/z*+ 300(M^+), 285, 268, 241, 223, 208, 181, 153, 152, 147, 119, 103, 91, and 77.

2-Butyl-2',4',6'-trimethylbenzophenone was obtained from the reaction of **Ib** with BuMgCl: IR(gas phase) ν 3022, 2935d, 2874, 1680(C=O), 1608, 1575(*ortho*-substituted phenyl mesityl ketone), 1447, 1386, 1248, 1174, 960, 909, 849, and 746 cm^{-1}. MS, *m/z*+ 280(M^+), 265, 237, 223, 208, 179, 147, 131, 119, 103, and 91.

4-Butyl-2',4',6'-trimethylbenzophenone was obtained from the reaction of either **Ib** or **Ia** with BuMgCl: IR(gas phase) ν 2937, 2873, 1684(C=O), 1607(*para*-substituted phenyl mesityl ketone), 1443, 1265, 1172, 960, 910, and 848 cm^{-1}. MS, *m/z*+ 280(M^+), 223, 208, 161, 147, 119, and 91.

Butylated 4-Bromo-2',4',6'-trimethylbenzophenone was obtained from the reaction of **Ia** with BuMgCl: IR(gas phase) ν 2935, 2875, 1680(C=O), 1583, 1467, 1387, 1426d, 1182, 1099, 960, 910, and 850 cm^{-1}. MS, *m/z*+ 360(M^+), 358, 345, 343, 316, 303, 301, 279, 222, 211, 209, 193, 147, 119, 102, and 91.

Di-Butyl-2',4',6'-trimethylbenzophenone was obtained from the reaction of **Ib** with BuMgCl: IR(gas phase) ν 2937, 2874, 1676(C=O), 1607, 1560, 1451, 1251, 1179, 965, 900, and 848 cm^{-1}. MS, *m/z*+ 336 (M^+), 321, 294, 279, 249, 223, 208, 193, 147, 119, 105, 91, and 77.

1-(4-Bromophenyl)-1-mesityl-1,3-butadiene was obtained from the reaction of **Ia** with allylmagnesium chloride: MS, *m/z*+ 328(M^+, Br^{81}), 326(M^+, Br^{79}), 303, 301, 247, 232, 217, and 183. IR(gas phase) ν

3086 (C=C-H), 2934, 1610, 1486, 1390, 1330, 1186, 1075, 1010, 918, 836, and 826. (no C=O absorption observed).

1-Phenyl-1-mesityl-1,3-butadiene was obtained from the reaction of **Id** with allylmagnesium chloride: ^{1}H NMR(200 MHz, $CDCl_3$) δ 7.30(m, 5H), 7.25(m, 1H), 6.80(s, 2H), 5.72(m, 1H), 5.20(dd, 2H), 2.21(s, 9H). MS, *m/z*$^+$ 248(M^+), 233, 225, 218, 105, and 77.

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Appendix I. Calibration of radical concentrations by standard 2,2-diphenyl-1-picryl hydrazyl (DPPH) free radical

Assuming that the relative intensity of overmodulated EPR signal does reflect the radical concentration, the relationship between the concentration of standard ([STD]) and the concentration of the radical species under investigation ([X]) can be established as follows:[28]

$$\frac{[X]}{[STD]} = \frac{A_X R_X (Scan_X)^2 G_{std} M_{std} (g_{std})^2 [S(S+1)]_{std}}{A_{std} R_{std} (Scan_{std})^2 G_X M_X (g_X)^2 [S(S+1)]_X} \qquad \text{(eq 1)}$$

A is the measured area under the absorption curve (this may be in arbitrary units as long as they are the same for unknown and standard).

Scan is the horizontal scale in Gauss per unit length on the chart paper.

G is the relative gain of the signal amplifier.

M is the modulation amplitude in gauss.

R is defined as $\sum_j D_j/D_k$ (D_k is the degeneracy of the most intense line and $\sum_j D_j$ is the sum of the degeneracies of all the lines in the spectrum) (for detail see ref. 28).