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NEW KETONE FRAGMENTATION PROBES FOR ELECTRON TRANSFER REACTIONS: THEIR REDUCTION MECHANISMS AND KETYL CLEAVAGE RATE MEASUREMENTS

BY

JIAN JEFFREY CHEN 

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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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **New Ketone Fragmentation Probes for Electron Transfer Reactions: Their Reduction Mechanisms and Ketyl Cleavage Rate Measurements**

submitted by **Jian Jeffrey Chen** in partial fulfilment of the requirements for the degree of the Doctor of Philosophy.

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(Supervisor)
Glen C. Russell
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TO MY PARENTS

ABSTRACT

The use of chemical probes to differentiate between polar ionic and electron transfer (ET) mechanisms is discussed. Several ketone fragmentation probes which give either the carbonyl reduction products (polar mechanism) or the fragmentation products of an α-substituent (ET mechanism) have been studied. α-Substituted acetophenones, $PhCOCH_2Y$ (Y = Br, Cl, F, OCOPh, $OCOCH_3$, OPh, SO_2Ar, and SPh), $PhCOCHMeY$ (Y = Br, Cl, F, SO_2Ar) and $PhCOCMe_2Y$ (Y = Br, Cl, SO_2Ar, SPh), are employed as probes to study the ET reactions of 1,3-dimethyl-2-phenylbenzimidazoline (DMBI) and triphenyltin hydride with ketones. Initiation, inhibition, and radical trapping experiments establish that the DMBI reductions of these α-substituted ketones to their corresponding ketones proceed via an ET hydrogen abstraction chain sequence. The DMBI reduction of the tertiary ketones ($PhCOCMe_2Y$) can be promoted by PhSH which acts as a chain transfer agent. The tin hydride reductions of $PhCOCH_2Y$ (Y = OCOPh, $OCOCH_3$, OPh, SO_2Ar, and SPh) are compared to the DMBI reductions and the possible involvement of ET processes in the tin hydride reductions is discussed.

The ring halogenated arylketones (XC_6H_4COR, X = H, Br, Cl; R = CH_3, Ph) are used as probes in the study of the ET reactions of both DMBI and sodium dithionite with ketones. The reactions with DMBI proceed via an ET mechanism whereas the reactions with sodium dithionite proceed via a nucleophilic addition mechanism.

Using the reported cleavage rate of *p*-bromoacetophenone ketyl as an ET clock the cleavage rate constants of the α-substituted acetophenone ketyls (k_{fY}) are measured from the intramolecular competitive DMBI reductions of several α-substituted *p*-bromoacetophenones (*p*-$BrC_6H_4COCH_2Y$, Y = Br, Cl, F, OCOPh, $OCOCH_3$, OPh). The cleavage rate constants for several ring halogenated acetophenone ketyls (k_{fX}) are determined indirectly from the intramolecular competitive reduction of disubstituted acetophenones ($XC_6H_4COCH_2Y$, X = *o*-Br, *p*-I, *m*-I; Y = OCOPh) using the measured k_{fY}.

α-Bromocamphor is used as a probe to study the ET reaction of *N,N*-dimethylaniline, triethylamine and ammonium formate with ketones. Initiation and inhibition experiments show that the reduction of α-bromocamphor to camphor proceeds via an ET hydrogen abstraction chain mechanism.

ACKNOWLEDGEMENTS

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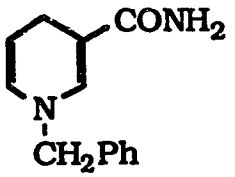
ABBREVIATIONS

The following abbreviations are used throughout the thesis:

AIBN — α,α'-azobisisobutyronitrile, $(CH_3)_2C(CN)-N=N-C(CN)(CH_3)_2$; a free radical initiator and used to initiate the free radical chain reductions.

AN — acetonitrile, CH_3CN; a solvent.

BNAH — *N*-benzyl-1,4-dihydronicotinamide; a reducing agent.



BNAH

BPO — di-*tert*-butylperoxide, $(CH_3)_3COOC(CH_3)_3$; a free radical initiator.

CIDNP — chemically induced dynamic nuclear polarization

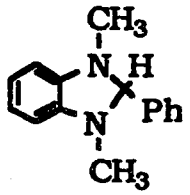
DBNO — di-*tert*-butylnitroxide, t-$Bu_2NO\cdot$; a radical chain inhibitor.

DBPO — di-*tert*-butylperoxyoxalate, $(CH_3)_3COO-COCO-OOC(CH_3)_3$; a room temperature radical initiator.

DCPH — dicyclohexylphosphine, $(c\text{-}C_6H_{11})_2PH$; a hydrogen atom donor.

DMA — *N*,*N*-dimethylaniline, $PhNMe_2$.

DMBI 1,3-dimethyl-2-phenylbenzimidazoline; a reducing agent.



DMBI

DMF dimethylformamide, $CH_3CON(CH_3)_2$; a solvent.

DMSO dimethylsulfoxide, CH_3SOCH_3; a solvent.

DNB *m*- or *p*-dinitrobenzene, $C_6H_4(NO_2)_2$; a strong electron acceptor and used to inhibit electron transfer chain reactions.

ee enantionmeric excess.

EPR electron paramagnetic resonance

ET electron transfer

GC gas chromatograph

GC-IR gas chromatograph-infrared spectroscopy

GC-MS gas chromatograph-mass spectroscopy

HLADH horse liver alcohol dehydrogenase

LAD lithium aluminum deuteride, $LiAlD_4$; a reducing agent.

LAH lithium aluminum hydride, $LiAlH_4$; a reducing agent.

NADH reduced nicotinamide adenine dinucleotide

NMR nuclear magnetic resonance

TEA teriethylamine, $N(C_2H_5)_3$.

THF tetrahydrofuran; a solvent.

UV ultraviolet absorption spectroscopy

CHAPTER 1

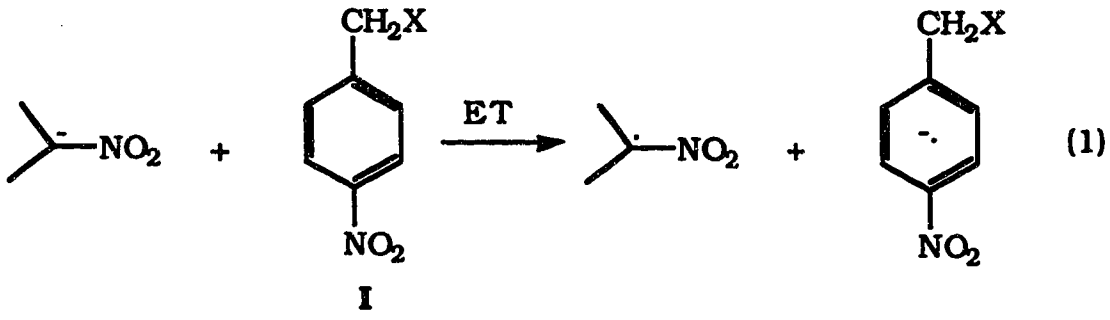
Chemical Probes for Electron Transfer Reactions

I-1. A Brief History of ET Reactions in Organic Chemistry

The studies of the single electron transfer reaction (SET or ET)[1] can be traced back to the nineteenth century. In 1891 Beckman and Paul[2] reported the formation of stable ketyls from the reaction of diaryl ketones and sodium. In 1916 Schlenk[3] proposed that aromatic ketones were reduced to pinacols by trityl sodium via an ET route. A similar ET mechanism was suggested for the reaction of aryl ketones with trityl Grignard reagents.[4] Extensive investigation of ET reactions in organic chemistry, however, did not start until the late 1950's.

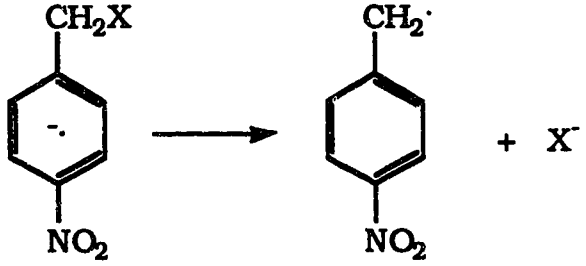
In the 1950's and 1960's an ET reaction was suggested as being involved in the autoxidation of carbanions[5] and Grignard reagents.[6] Russell reported the detection of stable radical anions in the ET reaction of various anions with unsaturated systems.[7] Kornblum's study on the alkylation of *p*-nitrobenzyl halides (I) with nitroparaffin salts triggered the extensive investigation of ET reactions in nucleophilic substitution reactions.[8] The O- and C-alkylation rates are affected differently by the leaving halide, and the C-alkylation reaction can be inhibited by nitrobenzene (NB) and dinitrobenzenes (DNB, *p*- or *m*-dinitrobenzene) with the order of inhibition *p*-DNB > *m*-DNB > NB. An ET nonchain mechanism was originally proposed for the C-alkylation reaction. Later, Kornblum[9] and Russell[10] independently proposed an ET chain sequence for the C-alkylation (Scheme I-1). This suggestion of a chain mechanism is largely based on the inhibitory effect of Cu^{2+}, DNB and oxygen.

initiation



(1)

propagation



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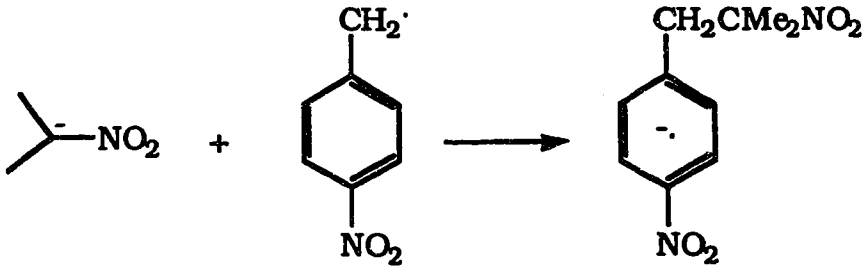

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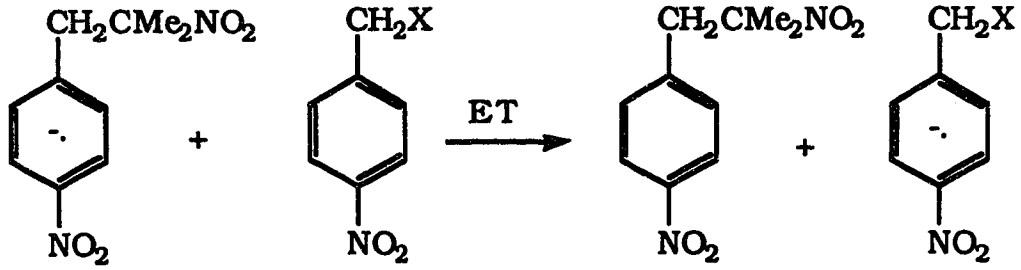
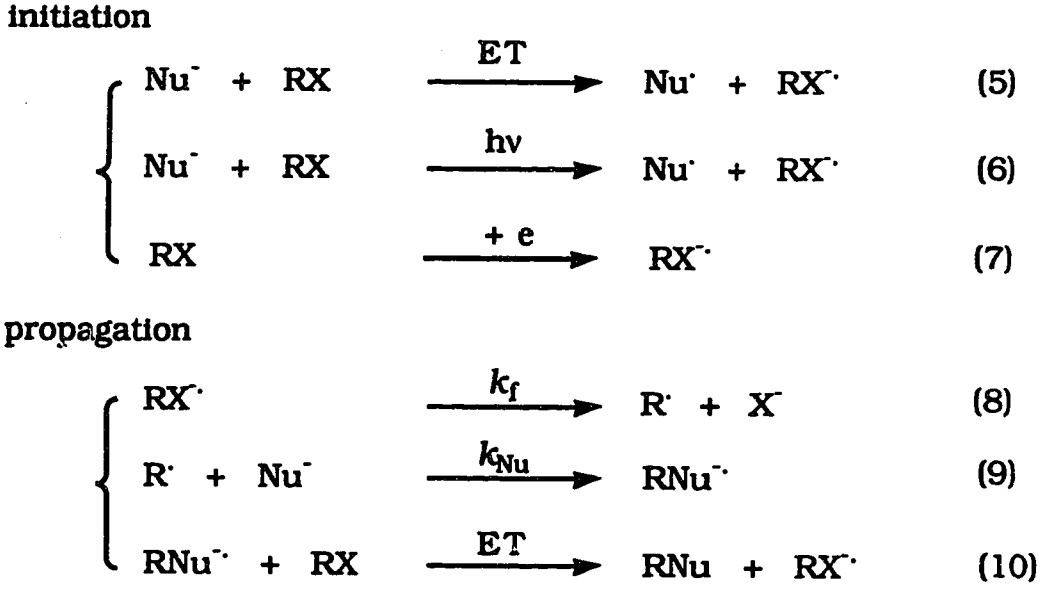


(4)

Scheme I-1. The Radical-Anion Free Radical Chain Mechanism for the Alkylation of the 2-Nitropropane Anion with *p*-Nitrobenzyl Halides

Following this proposal an extensive investigation of the scope of this type of radical anion-free radical chain reaction was undertaken. It has been established that a variety of electron acceptors and nucleophiles can undergo nucleophilic substitution reactions by this type of mechanism. Kornblum[11] and Russell[12] have comprehensively reviewed the subject. The reaction is generally believed to proceed via three chain propagation steps (Scheme I-2). The substrate radical



Scheme I-2. The $S_{RN}1$ Mechanism

anion ($RX^{-}\cdot$) cleaves to give the radical ($R\cdot$) and anion (X^{-}) (eq 8, Scheme I-2). The radical adds to the nucleophile (Nu^{-}) to produce an adduct radical anion ($RNu^{-}\cdot$) (eq 9, Scheme I-2) which in turn transfers an electron to the substrate to yield the substitution product

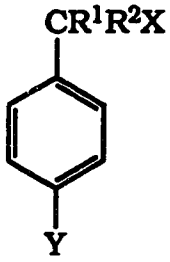
(RNu) and a new radical anion ($RX^{\cdot-}$) (eq 10, Scheme I-2). The chain reaction can be initiated by the direct ET from Nu^- to RX (eq 5, Scheme I-2), the photostimulated ET from Nu^- to RX (eq 6, Scheme I-2),[13] and the ET from the added initiator such as sodium to RX (eq 7, Scheme I-2).

An aromatic counterpart of this type of radical anion-free radical chain substitution reaction discovered by Bunnett,[14] has been extensively reviewed.[15] Bunnett used the symbol, $S_{RN}1$ (substitution, radical-nucleophilic, unimolecular), to describe this type of chain reaction due to the apparent similarity between eq 8-9 (Scheme I-2, RX = ArX) and the S_N1 mechanism. $S_{RN}1$ has subsequently been used to describe the radical anion-free radical nucleophilic substitution reactions in both aromatic and aliphatic systems (Scheme I-2). This designation does not, however, imply that the unimolecular cleavage of the substrate radical anion (eq 8, Scheme I-2) is rate-limiting in the chain sequence.

Compared to conventional S_N2 reactions, $S_{RN}1$ reactions are rather insensitive to steric hindrance and leaving group effects. Tertiary substrates and substrates with poor S_N2 leaving groups such as NO_2, SPh, OPh, and SO_2Ar[16] are especially suitable for this type of reaction since the competing S_N2 reactions are retarded. These reactions provide valuable routes for the synthesis of highly branched aliphatic compounds. A nitro substituent α to the leaving group is generally required for the aliphatic substrates to undergo $S_{RN}1$ reactions. The nitro group can be conveniently replaced by hydrogen upon treatment with organotin hydrides[17] and other hydride donors.[18] Typical

substrates (RX) and nucleophiles (Nu) that have been studied for aliphatic $S_{RN}1$ reactions are listed below (for a detailed list see ref. 12).

RX :



$Y = NO_2$, CN, SO_2Ph
R^1, R^2 = H, CH_3
X = Cl, Br, NO_2, SPh, OPh, NMe_3^+, OCOPh

$Y = NO_2$, CN, SO_2Ph, SPh, CO_2Et
R^1, R^2 = alkyl
X = Cl, Br, NO_2

Nu^- : $R^1R^2CNO_2^-$, $R^1R^2C{=}C(O^-)Ph$, $RC(CO_2Et)_2^-$, ArS^- $ArSO_2^-$, $(EtO)_2PO^-$, $RCOCHCOR^{1-}$, etc.

Leaving group X :

Cl, Br, NO_2, SPh, SO_2Ar, OPh, NMe_3^+, OCOPh, etc.

Despite extensive investigation of $S_{RN}1$ reactions, several fundamental questions still exist: what conditions are required for the reaction to occur and which step is rate-limiting? Except for aromatic substrates, there are few kinetic studies of the overall reactions and of individual steps.

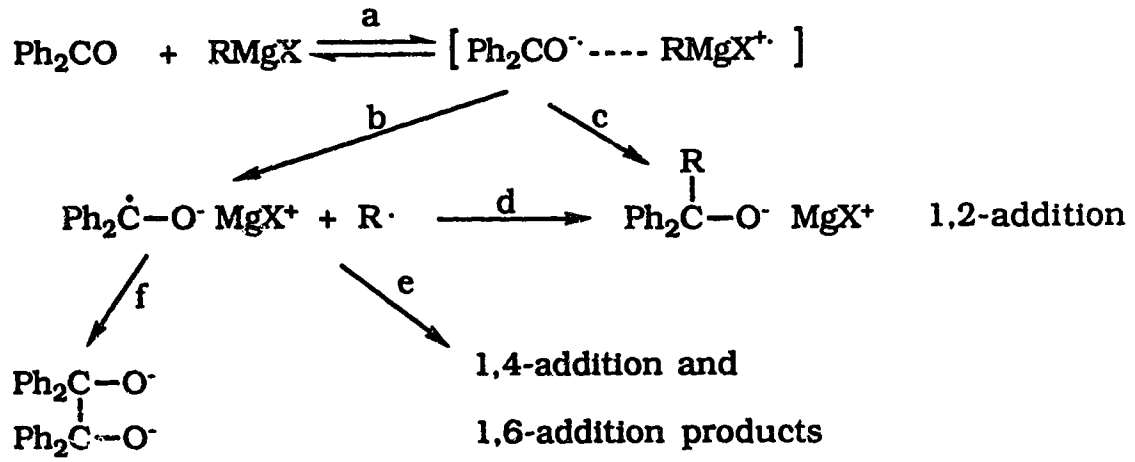
Aromatic $S_{RN}1$ reactions can be effected by direct electrochemical stimulation (eq 7-10, Scheme I-2, RX = ArX).[19] The reduction potential of the substrate (ArX), and the cleavage rate constant (k_f) of the radical anion ($ArX^{-\cdot}$) can be directly measured by the electrochemical reduction of ArX.[20] K_f can also be obtained by pulse radiolysis.[21] The rate constants for the reaction of aryl radicals with nucleophiles (k_{Nu}) can be determined by electrochemical methods.[22] These reactions are rare examples of ET chain reactions where the rate constant of each elementary step is known.

Many classical organic reactions classified as polar ionic reactions have been subsequently studied to determine whether these reactions proceed via ET pathways. At least two alternative pathways, ET nonchain and $S_{RN}1$ chain sequences, are possible for classical S_N2 reactions.[23] The $S_{RN}1$ chain process can be easily identified by initiation and inhibition studies.[24] The ET nonchain and S_N2 processes are difficult to distinguish, and research has been directed at the detection of intermediate radicals by using a variety of chemical probes (vide infra). The nucleophilic addition to enones was investigated by House in the 1970s for the possible involvement of ET reactions.[25] These studies have been instrumental to the subsequent understanding of the ET mechanism proposed for the reactions of ketones.

ET reactions are believed to be involved in some of the reactions of Grignard reagents with ketones. As early as 1929, Blicke and Powers proposed an ET pathway to account for the formation of side products (pinacol and the reduction product) in the Grignard reaction with

benzophenone.[26] After the detection of ketyls by EPR spectroscopy during the reactions of the Grignard reagents with substituted benzophenones,[27] the radical nature of the reaction has been investigated using a variety of techniques.[28]

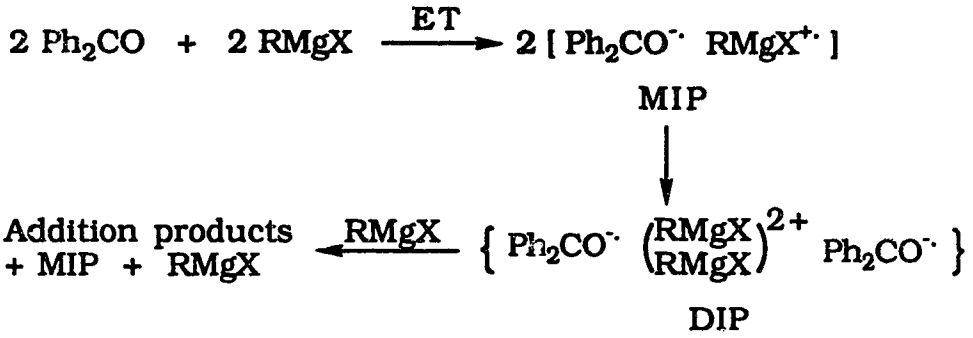
From the studies of the substituent effect in the reaction of *tert*-butylmagnesium chloride with substituted benzophenones, and from the observation of a different reactivity order of RMgX towards benzophenone and acetone (R = *t*-Bu > *i*-Pr > Et > Me for Ph_2CO; Me > Et > *i*-Pr > *t*-Bu for acetone), Holm[29] concluded that the reaction of RMgX with benzophenones proceeds via an ET pathway. Ashby[30] proposed a similar ET pathway (Scheme I-3) based on his investigations using EPR spectroscopy, reaction kinetics and chemical probes.



Scheme I-3

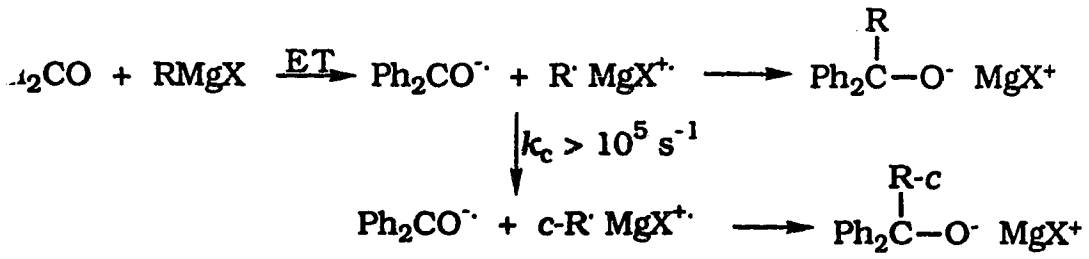
In the proposed mechanism two intermediates are involved, and the normal addition product (1,2-addition) comes from the cage

coupling of the radical pairs (Scheme I-3). From the analysis of the observed EPR and UV spectra of radical intermediates Maruyama[31] proposed that two types of radical ion pairs (monomeric, MIP, and dimeric, DIP) are involved in the Grignard reactions of benzophenone, benzil, and fluorene (Scheme I-4). Walling[32] presented a kinetic



Scheme I-4

analysis of the Grignard reaction, and suggested that cage coupling is not necessary to account for the production of the 1,2-adduct in high yield. The radicals (R·) formed have enough time to undergo a rearrangement which has a rate constant larger than 10^5 s^{-1}. The rearranged radical (*c*-R·) can then couple with the ketyl to yield the addition product (Scheme I-5). More recently, Yamataka[33]

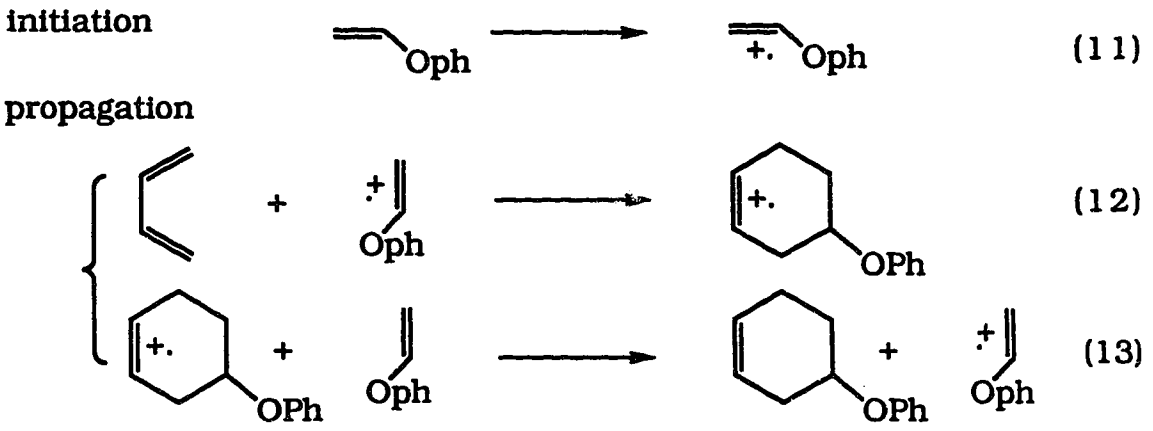


Scheme I-5

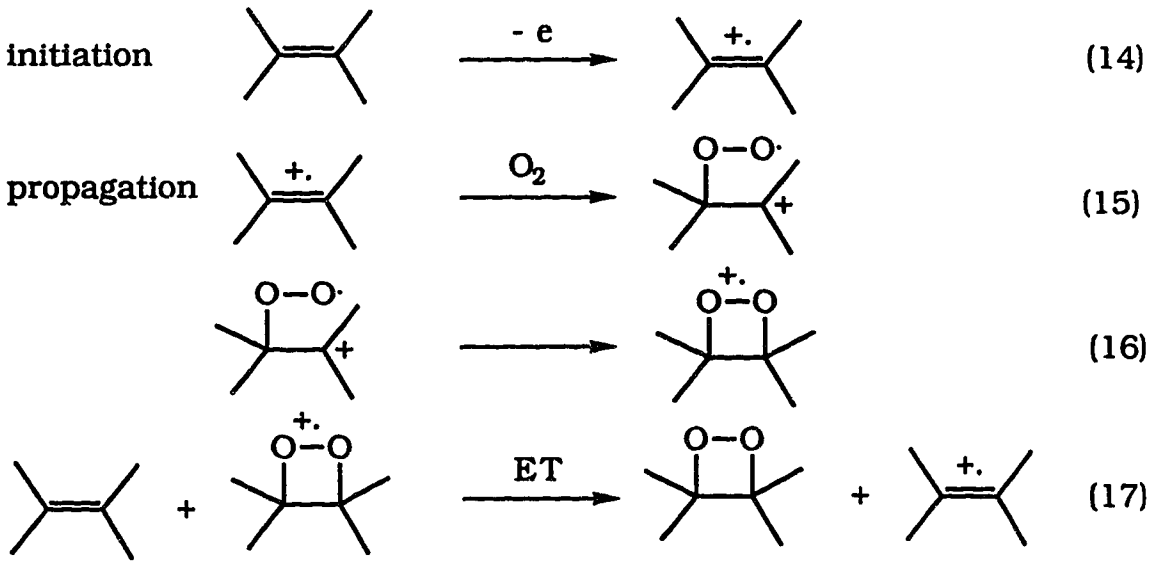
suggested that the $^{14}C/^{12}C$ isotope effect can be used to determine the rate-limiting steps in the ET reactions of benzophenone with Grignard reagents. It should be pointed out that our understanding of the detailed mechanisms of Grignard reactions is still limited, and conflicting evidence has been reported by various investigators. Most studies reported so far have focused only on the reactions of diaryl ketones.

Many other classical organic reactions have been examined for the involvment of ET pathways: the Meerwein-Pondorff-Verley reduction,[34] the Aldol condensation,[35] the Cannizzaro reaction,[36] the Claisen condensation,[37] the Wittig reaction,[38] and the reduction of ketones by metal hydrides.[39] Most of these studies rely only on isolated experimental observations. The mechanistic explanations should be subject to further investigation before ET reactions are considered as general reaction pathways for these reactions.

In the last few years, an increasing number of papers have suggested the formation of radical cation intermediates as part of chain sequence. The catalyzed cycloaddition of olefins can proceed through an ET chain sequence under chemical, electrochemical, or photochemical initiation (scheme I-6).[40] Tris(*p*-bromophenyl)-ammonium hexachloroantimonate and other triarylammonium radical cations are especially good ET initiators for radical cation chain reactions.[41] The oxygenation reaction of olefins[42] can proceed through a radical chain sequence involving radical cation intermediates (Scheme I-7). Radical cations have also been suggested as being involved in a number of photoinduced ET reactions.[43] Aromatic



Scheme I-6. The Radical Cation Cycloaddition of Olefins



Scheme I-7. The Radical Cation Oxygenation Reaction of Olefins

nitrations,[44] and other electrophilic aromatic substitution reactions[45] ha e been recently proposed to proceed via an ET nonchain mechanism involving radical cation intermediates.

Recently theoretical treatments of ET reactions have been developed. The Marcus equation[46] has been used to analyze ET reactions in both organic[47] and organometallic[48] chemistry. Pross proposed that the single electron shift is a fundamental process in organic chemistry and can be used to describe both polar and ET processes.[49] The valence bond curve crossing model was used to analyze the organic ET reaction between a radical anion and an even-electron species.[50] In this type of ET reactions, the inner-sphere mechanism is inherently preferred over the outer-sphere mechanism.

Electron transfer reactions are involved in a variety of fields: photochemistry,[51] electrochemistry,[52] photoelectrochemistry,[53] organometallic chemistry,[54] radiation chemistry,[55] coal liquefaction,[56] metabolism of toxic chemicals,[57] and biological chemistry.[58]

In order to substantiate the involvement of ET reactions, many unique approaches have been developed in the past few decades.[59] EPR spectroscopy has been used extensively to detect stable radicals or radical ions. It does not provide any definitive information on how these paramagnetic species are formed, and care must be taken to extract mechanistic information from EPR results.[60] Spin trapping[61] can be employed to detect unstable radicals formed during ET reactions by EPR and NMR spectroscopic techniques.[62] Radical intermediates can also be trapped by reagents such as olefins, oxygen, and nitroxides to give stable products which can be identified. From such trapping studies, it is possible to derive rate constants of the competing reactions of the radical being trapped.[63] Chemically induced magnetic nuclear polarization effect (CIDNP) has also been

used to detect radical intermediates in ET reactions.[64] Deuterium[65] and carbon[66] isotope effects have been used to differentiate between ET and polar ionic pathways and to determine the rate-limiting step in the overall reaction sequence. More recently ET reaction rate constants have been theoretically calculated using the Marcus equation.[46] The calculated rate constants were compared with experimentally observed rate constants in order to determine whether the ET reactions are feasible.[67]

The most convenient method used to establish the involvement of ET reactions is to employ a chemical probe. A chemical probe can be defined as either a reagent or substrate which, upon ET, produces an intermediate (radical ion or radical) that undergoes a very rapid radical reaction to give a radical-derived product. The advantage of a chemical probe is that it allows the reaction to be analyzed quantitatively since the rate constant of the secondary radical reaction is often known.[68] The chemical probes can be divided into three categories according to the nature of the secondary radical reaction: the stereochemical probe, the radical rearrangement probe, and the fragmentation probe.

In this chapter we will discuss these chemical probes with emphasis on the pitfalls of using these probes to identify an ET mechanism. This review is not intended to be comprehensive but rather selective. Our aim is to identify possible problems among existing reports and to suggest directions for further research.

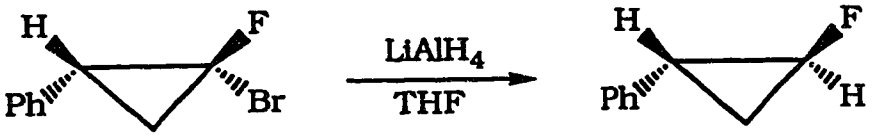
I-2. Chemical Probes for ET Reactions

A. Stereochemical Probes

Organic radicals are generally considered to be planar or pyramidal with rapid inversion.[69] The inversion rate of free radicals decreases with the increasing s character of the semioccupied orbital. The configurational stability of the radicals has the order: vinyl radicals (sp^2-hybridized) > cyclopropyl radicals ($sp^{2.5}$-hybridized) > acyclic radicals (sp^3-hybridized).[70] The inversion rate (and inversion barrier) is affected significantly by the α-substituent; electronegative groups, particularly fluorine, reduce the inversion rate.[71] The loss of the stereochemical integrity at the reaction center can be used as evidence for the involvement of a free radical intermediate (and thus an ET reaction) although other experimental tests are required to substantiate the radical intermediacy.

Cyclopropyl radicals have an inversion rate of 10^6 - 10^{11} s^{-1}.[72] α-Chloro and fluorocyclopropyl radicals were estimated as having an inversion rate of 2 x 10^7 s^{-1} [73] and 10^6 s^{-1}.[74] Retention of stereochemistry has been observed in the reaction of these α-substituted cyclopropyl radicals with radical scavengers such as tin hydrides, bromine, and bromochloroform. Therefore the retention of stereochemistry in the reaction of cyclopropyl derivatives cannot be used as exclusive evidence to rule out the involvement of cyclopropyl radical intermediates.

Stereochemical probes have been used to study reaction mechanisms for the reduction of halocyclopropanes with metal hydrides. The reduction of *gem*-bromofluorocyclopropanes with lithium aluminum hydride (LAH) yields fluorocyclopropanes with retention of configuration (eq 18). A four-center mechanism was proposed to account for the stereoselectivity (Scheme I-8).[75] A



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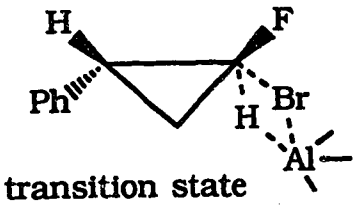
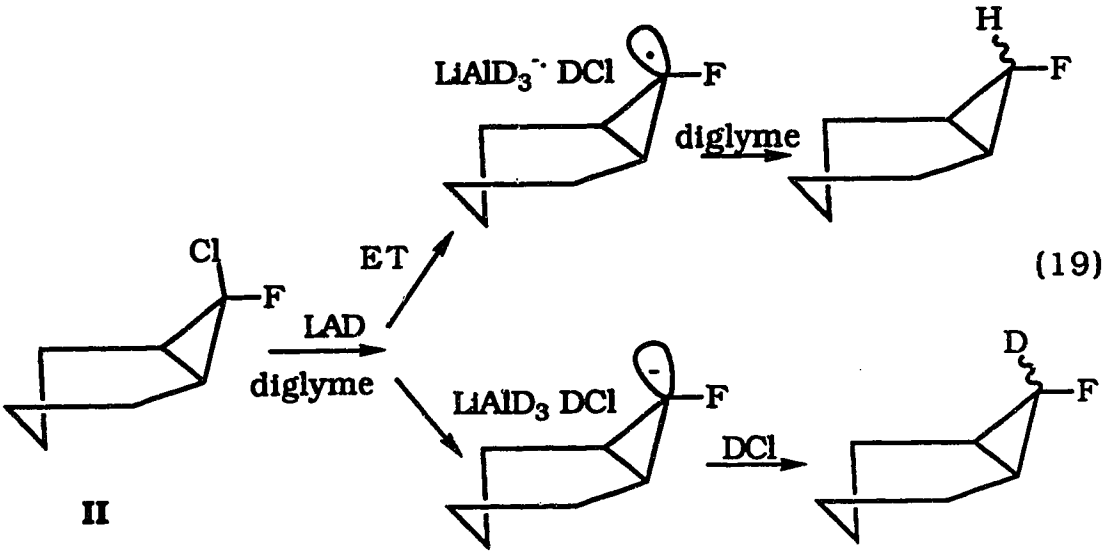
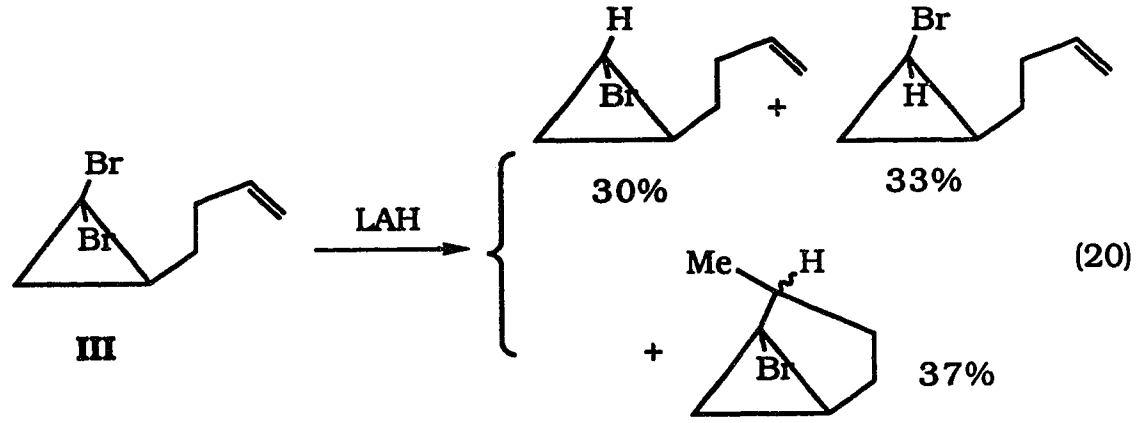


Scheme I-8

cyclopropyl carbanion was suggested as the intermediate in the reduction of *gem*-dibromo or dichlorocyclopropanes to the corresponding monohalocyclopropanes since the reduction product of the *gem*-chlorofluorocyclopropane (**II**) by lithium aluminium deuteride (LAD) is 100% monodeuterated (eq 19).[76] In addition to the normal reduction products, cyclized products were also observed in the reduction of a cyclizable probe, **III** (eq 20). This result suggests the involvement of a free radical intermediate.[77]



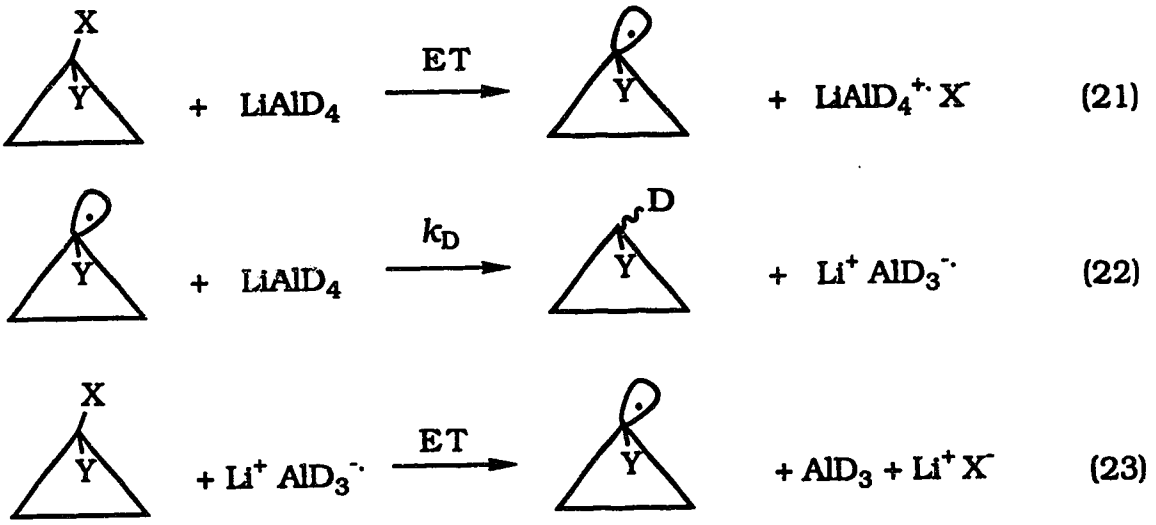
(19)



(20)

If the reduction of *gem*-dihalocyclopropanes by LAH does proceed via the α-halocyclopropyl radical intermediate, then the retention of stereochemistry in the reduction of *gem*-bromofluorocyclopropanes may be accounted for by assuming that the hydrogen atom abstraction by the cyclopropyl radical from LAH (k_H) is faster than the ring inversion (k_{in}). The absolute deuterium incorporation (100%) in the reaction of **II** with LAD may be the result of a faster hydrogen

abstraction from LAD than from the solvent. The possibility of a free radical **chain** mechanism (eq 21-23, Scheme I-9) has neither been mentioned nor investigated for these reductions by LAH, even though



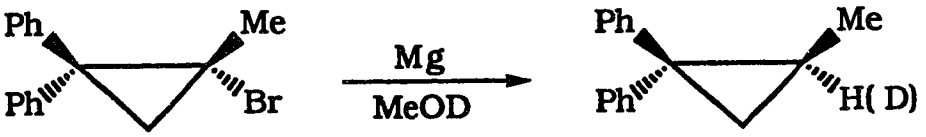
X = Br, Cl; Y = Br, Cl, F

Scheme I-9. The Possible ET Mechanism for the Reduction of Cyclopropyl Halides by Lithium Aluminum Deuteride

the reduction of *gem*-dibromocyclopropanes by $NaBH_4$ proceeds by a radical **chain** process.[78] The radical ($Li^+AlD_3^{-}\cdot$) formed upon hydrogen abstraction from LAD has been reported to react with alkyl halides to produce alkyl radicals.[79] The ET from $Li^+AlD_3^{-}\cdot$ to *gem*-dihalocyclopropanes (eq 23, Scheme I-9) is therefore feasible. A similar chain mechanism was suggested for the reduction of aryl bromides with LAH.[80] The hydrogen abstraction by aryl and cyclopropyl radicals has a similar rate constant.[81] These results argue for the proposed ET

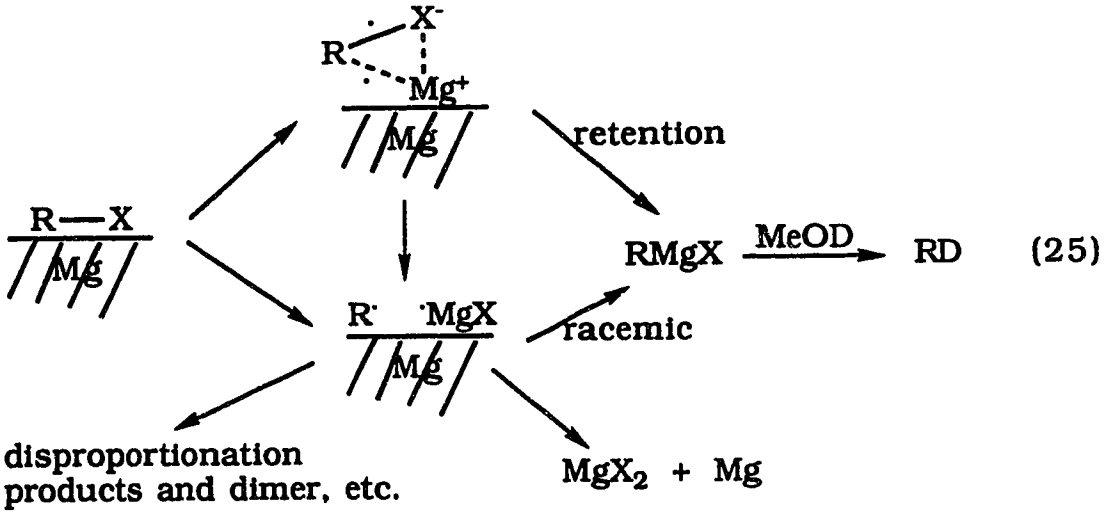
chain mechanism in the reduction of *gem*-dihalocyclopropanes by LAH or LAD. Free radical chain initiators and inhibitors can be used to establish whether this chain reaction is operative.

(S)-(+)-1-Bromo-1-methyl-2,2-diphenylcyclopropane ((S)-IV) has been used extensively as a stereochemical probe to study ET reactions of cyclopropyl halides.[72a-b] From the observation of a certain degree of retention of stereochemistry in the reaction of (S)-IV with magnesium (eq 24)[82] and other metals,[72a-b] it was suggested that the cyclopropyl radical formed from an ET between Mg and (S)-IV is absorbed on the metal surface (eq 25) and can retain its stereochemical identity. In



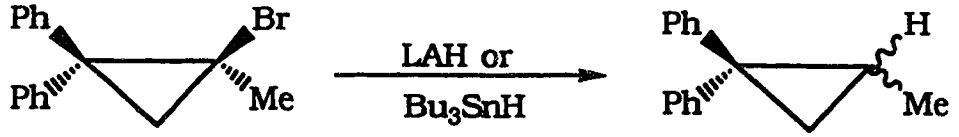
(24)

(S)-IV

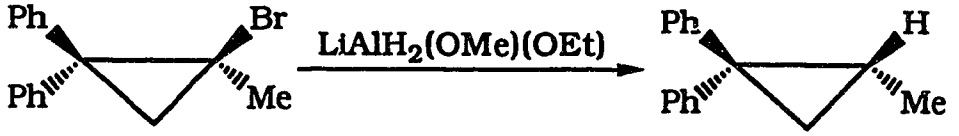


(25)

contrast, the radicals formed in the reaction of alkyl halides with Mg diffuse freely in the solution.[83] The inversion rate of the α-methylcyclopropyl radical is 2 x 10^{11} s^{-1} at 71 °C,[84] and is faster than most radical trapping reactions. The racemic products are therefore expected from optically active α-methylcyclopropyl halides if the reaction goes through the α-methylcyclopropyl radical intermediate. The reduction of (*R*)-(-)-1-bromo-1-methyl-2,2-diphenylcyclopropane **(*R*)-IV** by LAH and *n*-Bu_3SnH yields the same racemic products (eq 26), whereas the reduction by sodium methoxyethoxyaluminium hydride (SMEAH) gives the product with the retention of configuration (eq 27).[85] These results suggest that the reduction by LAH and *n*-Bu_3SnH proceeds through the cyclopropyl radical intermediate while the reduction by SMEAH proceeds through the cyclopropyl carbanion intermediate.



(*R*)-IV racemic (26)

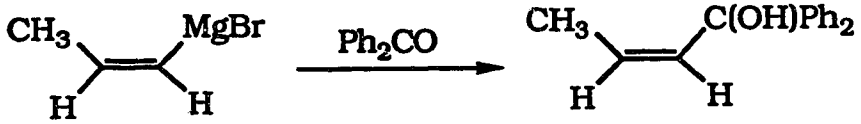


(*R*)-IV retention (27)

Vinyl radicals exist either as "bent" σ radicals or "linear" π radicals. The inversion of σ radicals is very fast (10^7 - 10^9 s^{-1}).[70] Although certain substituted vinyl radicals can be trapped by efficient radical

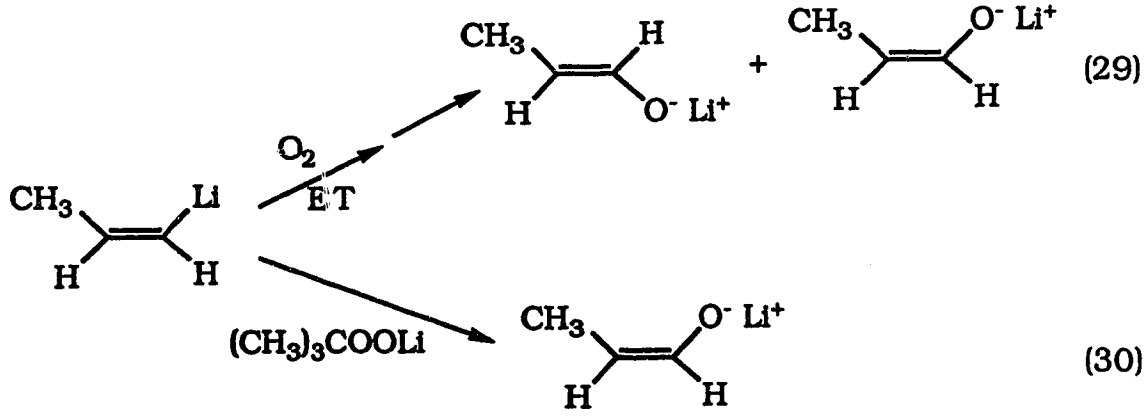
scavengers such as tin hydrides and oxygen with a certain degree of retention of configuration, the loss of the stereochemical integrity of the olefin through the vinyl radical intermediate is observed in most reactions and this observation might be used as a diagnostic tool for the involvement of vinyl radicals.

cis-Propenylmagnesium bromide was used as a stereochemical probe to study its possible ET reaction with benzophenone.[86] The 1,2-addition product retains the stereochemical integrity of the vinyl group (eq 28). This result indicates that the propenyl radical is not



(28)

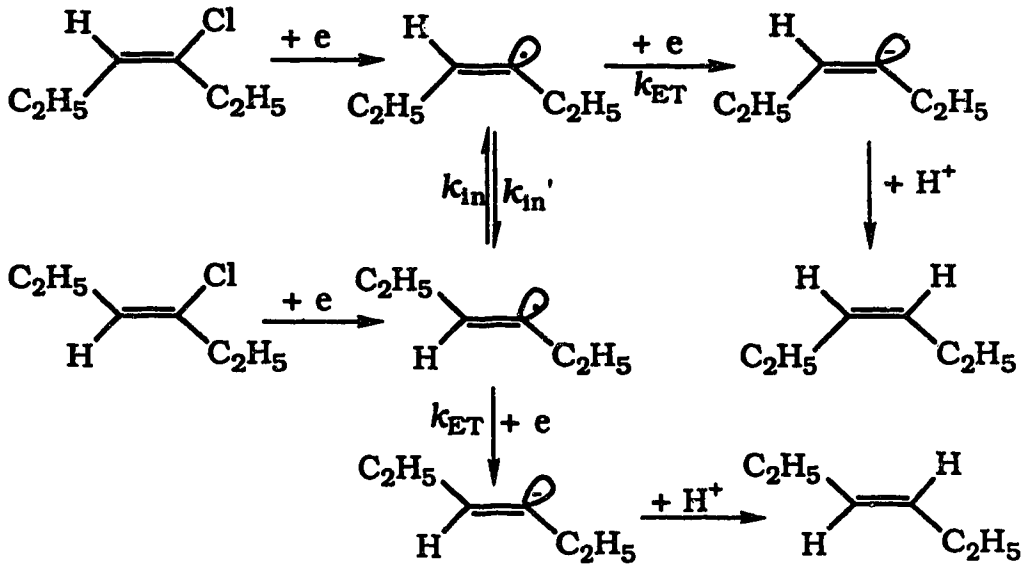
involved in this Grignard reaction. The reaction of *cis*-propenyllithium with oxygen at -78 °C yields the corresponding lithium enolate with partial loss of stereochemistry around the double bond (eq 29),[87] but the reaction with lithium *tert*-butylperoxide yields the lithium enolate with retention of configuration (eq 30). These results suggest that the propenyl radical is involved in the reaction with oxygen, but not in the reaction with *t*-BuOOLi.



(29)

(30)

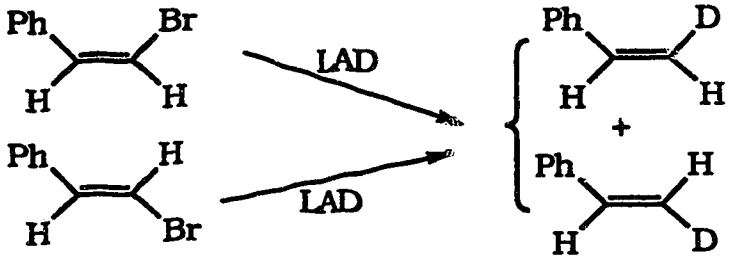
The reaction of both *cis* and *trans* 3-chloro-3-hexene with sodium naphthalenide leads to the predominant formation of *trans*-3-hexene. The ratio of *trans* to *cis* 3-hexene depends on the configuration of the vinyl chloride used. The reaction sequence shown in Scheme I-10 was proposed to account for the stereochemical results.[88] An ET reaction from sodium naphthalenide to *cis*-3-chloro-3-hexene gives the *cis*-3-hexenyl radical. The *cis* vinyl radical can undergo a second ET



Scheme I-10

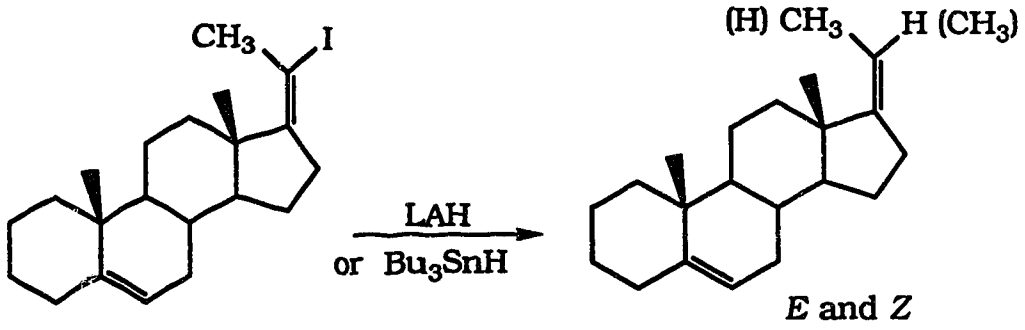
reaction to yield the configurationally stable vinyl carbanion or undergo an inversion to give the more stable *trans* vinyl radical. A similar reaction sequence was also suggested for the electrochemical reduction of *cis* and *trans* 3-iodo-3-hexene.[89] Chung[90] studied the reduction of *cis* and *trans* styryl bromide by LAD in THF. The same mixture of *cis* and *trans* styrenes was obtained from both styryl

bromides (eq 31). This result seems to indicate that the styryl radical



(31)

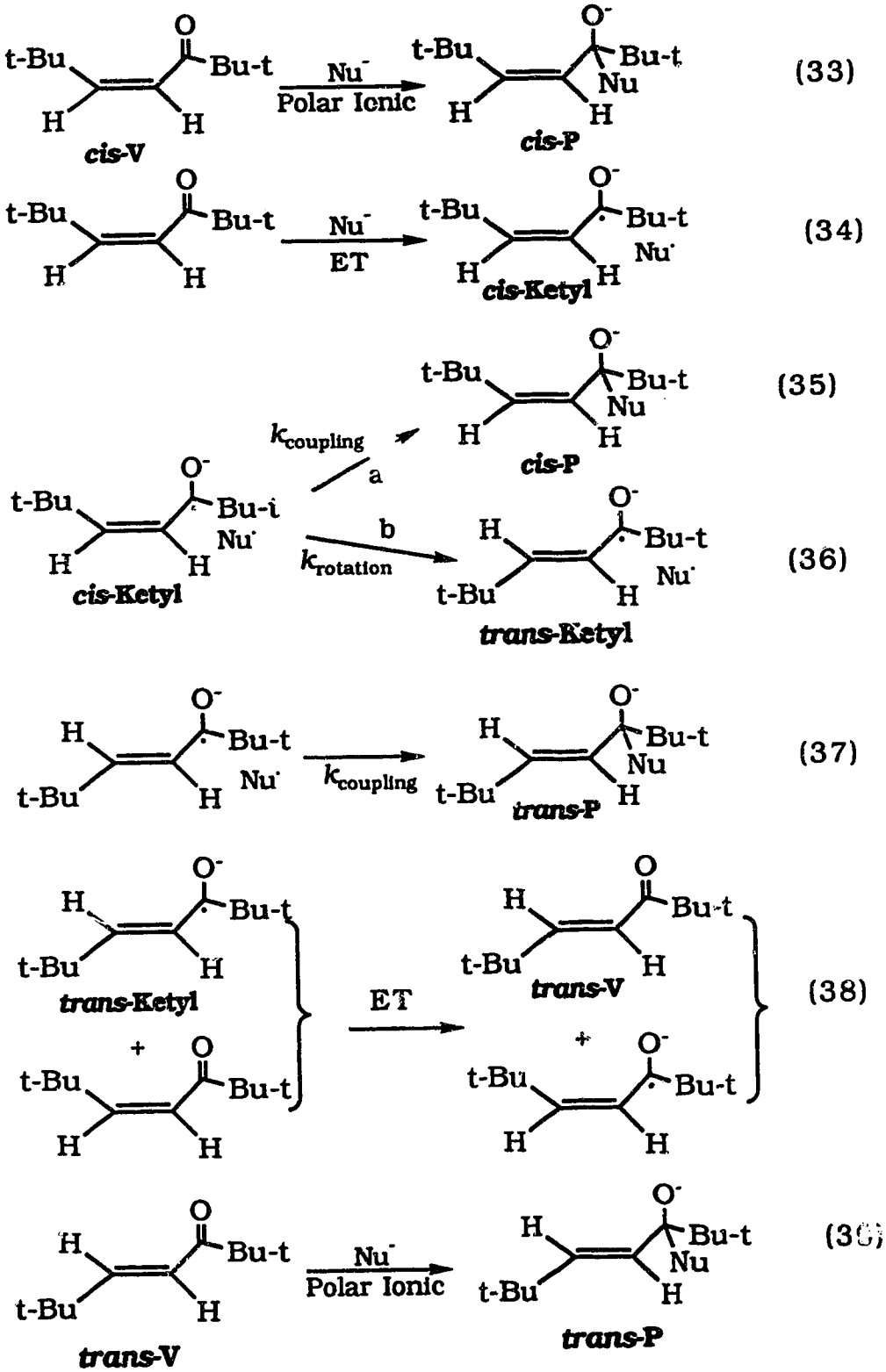
is an intermediate in the reaction sequence. A similar result was observed in the reduction of a steroidal vinyl iodide with LAH and *n*-Bu_3SnH (eq 32).[91] As in the reduction of *gem*-dihalocyclopropanes by



(32)

LAH, it is still not clear whether the reduction of vinyl halides by LAH proceeds through a radical chain or a radical nonchain mechanism.

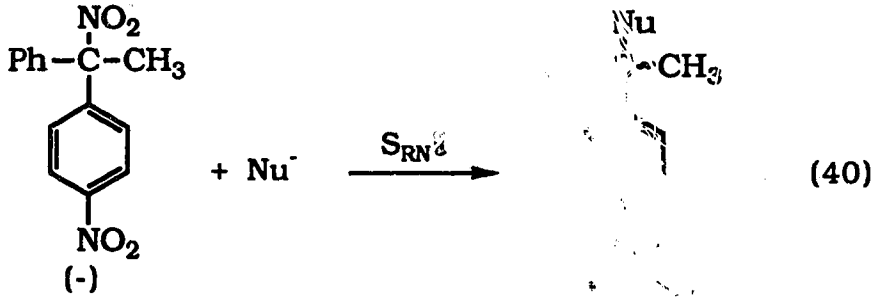
cis-2,2,6,6-Tetramethylhept-4-en-3-one (***cis*-V**) has been used as a stereochemical probe for the involvement of ET reactions in the reaction with organometallic reagents (RMgX, RLi, Me_2CuLi)[92] and the superoxide ion.[93] A polar ionic reaction of ***cis*-V** with a reagent (Nu^-) gives the *cis* addition product (eq 33, Scheme I-11). An ET from Nu^- to ***cis*-V** produces the *cis* radical anion (eq 34, Scheme I-11) which isomerizes rapidly to give the more stable *trans* radical anion (eq 36).



Scheme I-11. The Possible Reactions of the Probe *cis*-V with Nu⁻

Further reactions of this *trans* radical anion yield a *trans* addition product (eq 37, Scheme I-11). The formation of this *trans* product is then used as evidence for the ET reaction. If the ET from the *trans* radical anion to ***cis*-V** to yield the *trans* enone and the *cis* radical anion (eq 38, Scheme I-11) is rapid, the *cis* enone can be rapidly converted to the *trans* enone by an ET chain process.[92] The polar ionic reaction of the *trans* enone would also produce the same *trans* addition product (eq 39, Scheme I-11). Therefore results obtained from ***cis*-V** cannot lead to any definite conclusions concerning the reaction mechanisms.

The $S_{RN}1$ reaction of optically active *p*-nitrocumyl derivatives gives completely racemized substitution products (eq 40).[94] Similarly, chiral stannanes lead to racemic products in reactions with $CpFe(CO)_2^-$ and metal hydrides (eq 41-42).[95] The racemic products are presumably formed through a triorganostannyl radical intermediate ($R_3Sn\cdot$). The



(40)

$Nu^- = N_3^-, PhS^-, (CH_3)_2CNO_2^-$

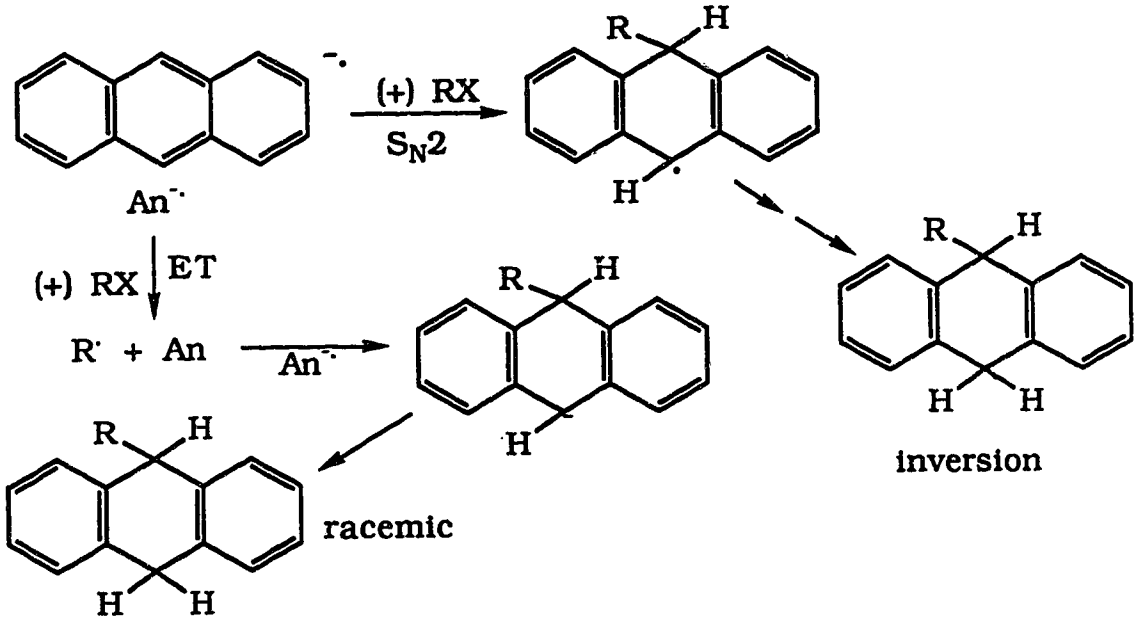
$$Me(PhMe_2CCH_2)PhSnCPh_3 \xrightarrow{Cp(CO)_2Fe^-} Me(PhMe_2CCH_2)PhSnFe(CO)_2Cp \quad (41)$$

(-) racemic

$$Me(PhMe_2CCH_2)PhSnCPh_3 \xrightarrow{LAH} [Me(PhMe_2CCH_2)PhSn]_2 \quad (42)$$

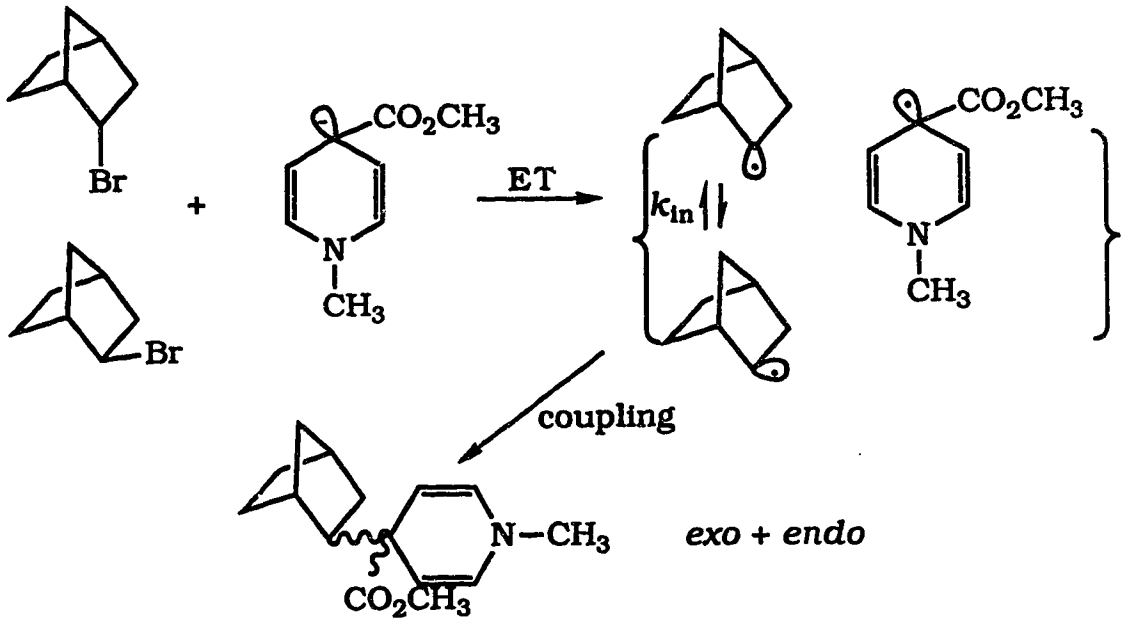
(+) racemic

reaction of anthracene radical anions with optically active alkyl halides produce mainly racemic products with a certain degree of inversion (1-40%). It was suggested that the racemic product is formed by an ET pathway whereas the product with net inversion is formed by an S_N2 reaction (Scheme I-12).[96] A similar stereochemical result was observed in the alkylation of benzophenone ketyl with alkyl halides.[97]



Scheme I-12

The reaction of both bornyl and isobornyl bromides with the enolate of 4-methoxycarbonyl-1-methyl-1,4-dihydropyridine gives both *exo* and *endo* substitution products (Scheme I-13); the ratio of *exo* to *endo* products depends upon the configuration of the starting bromide.[98] The reaction of the same enolate with 6-halo-6-metnyl-1-heptene gives no cyclized products. These results show that radical

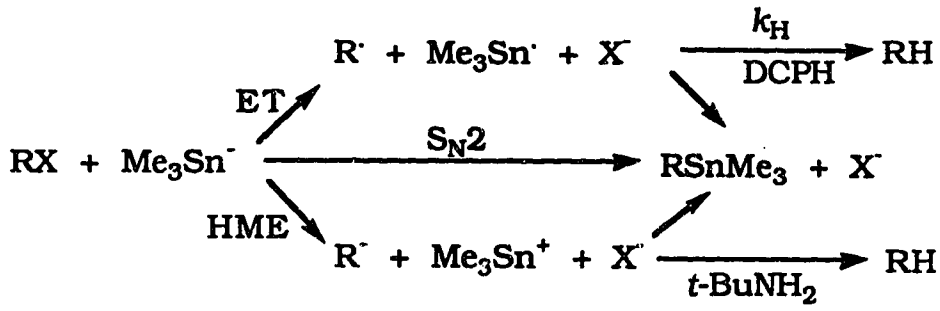


Scheme I-13

coupling in the solvent cage is competitive with the radical inversion but is much faster than the radical cyclization ($k_c \approx 10^{5\text{-}6}\ s^{-1}$).

The reaction of (triorganostannyl)alkalies (R_3SnM) with organic halides to yield tetraorganostannanes (R_4Sn) has attracted much attention in the last two decades. A variety of stereochemical studies, trapping experiments and radical rearrangement probes have been used to delineate the reaction mechanisms. Despite these studies, exact mechanisms are still not clearly defined. The reaction of the optically active 2-butyl bromide and chloride with Ph_3SnNa proceeds with complete inversion of configuration, and a S_N2 process was suggested.[99] The reaction of 4-*tert*-butyl cyclohexyl bromide with Me_3SnM (M = Li, Na, K), however, yields nonstereospecific products.[100] This result indicates that other competing reaction pathways besides the S_N2 reaction are involved. Kuivila[101] used

trapping experiments to differentiate between ET, S_N2 and HME (halogen-metal exchange) pathways. Dicyclohexylphosphine (DCPH) was used to trap radicals and *t*-$BuNH_2$ was used to trap carbanions (Scheme I-14). It was concluded that the reaction of a primary alkyl



Scheme I-14

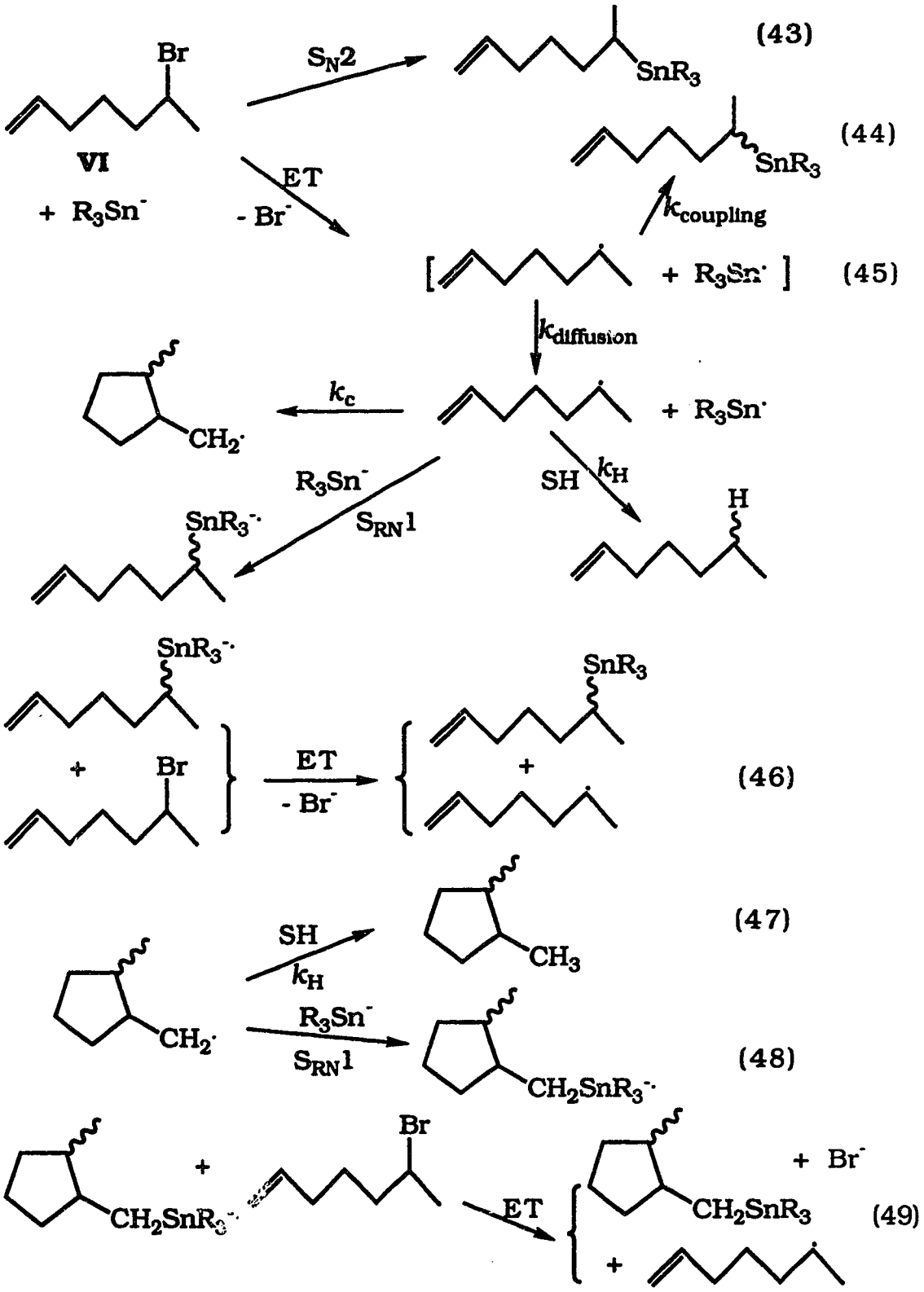
bromide proceeds only by an S_N2 mechanism, but the reaction of a secondary alkyl bromide such as 2-bromooctane proceeds by competing S_N2, ET, and HME mechanisms. San Filippo[102] reported that the reaction of (-)-2-bromooctane proceeds with predominant (> 90%) inversion of configuration, and concluded that the S_N2 reaction is the major reaction pathway. These results are not in agreement with Kuivila's trapping results. San Filippo suggested that the use of DCPH in Kuivila's study introduces substantial perturbation on stereoselectivity and product distribution, and that the trapping results cannot be used to establish the reaction mechanism in the absence of the trapping agents.

Kuivila[103] reinvestigated the reaction of 2-bromooctane and found that the product distribution and stereochemistry depend on the nature of the cation (M^+) and on the coordinating ability of the solvent.

The S_N2 mechanism competes most efficiently in good coordinating solvents. Contrary to San Filippo's report, the reaction of (+)-2-bromooctane with Me_3SnNa in THF gives the substitution product with only 50% ee, and the addition of DCPH slightly increases the ee. In the presence of DCPH the yield of the substitution product decreases from 60% to 10% and yield of the reduction product increases from 26% to 85%. Therefore 10% (out of 60%) of the substitution product is formed by a S_N2 pathway, whereas the rest (50% out of 60%) of the substitution product is formed from a radical intermediate which could be trapped by DCPH to give the reduction product. If the radical intermediate is a free 2-octyl radical, the substitution product derived from the 2-octyl radical would be racemic and the net optical purity of the substitution product in the absence of DCPH would only be (60-50)/60, i.e. 16.7% ee. Experimentally, the optical purity is found to be 50%. Those intermediates that are trapped by DCPH to give the reduction product would provide a substitution product with excess inversion (40% ee). Since the trapping rate constant of the 2-octyl radical by DCPH is 1×10^6 M^{-1} s^{-1} [104] and since the radical intermediate loses its stereochemical identity at a slower rate than the radical trapping by DCPH, the inversion rate of the radical intermediate formed in the reaction of 2-bromooctane with Ph_3SnNa in THF is less than 1×10^6 s^{-1} (assuming that the concentration of DCPH is 1 M).[103]

Ashby[105] studied the reaction of 6-halo-1-heptenes and optically active 2-halooctanes with Me_3SnNa in THF. Substantial amounts of cyclized products were observed in the reaction of 6-bromo-1-heptene

(VI). Addition of DCPH diverts the cyclized reaction products to the straight chain hydrocarbon. These results clearly show that radical intermediates are involved in the reaction. The formation of cyclized substitution product is inhibited by radical chain inhibitors, *p*-dinitrobenzene (DNB) and di-*tert*-butylnitroxide (DBNO). This observation seems to suggest an $S_{RN}1$ mechanism for the formation of the substitution product (eq 45, 48, and 49, Scheme I-15). An $S_{RN}1$ mechanism was also suggested for the trimethylstannylation of 1,4-dihalobicyclo[2.2.1]heptanes.[106] Newcomb,[107] however, argued that the reaction of alkyl radicals with Me_3Sn^- (eq 48, Scheme I-15), a key step in the $S_{RN}1$ chain sequence, is unlikely since the adduct $Me_3SnR^{-\cdot}$ is extremely unstable. The $S_{RN}1$ mechanism, however, is still possible if the ET from $Me_3SnR^{-\cdot}$ to RX (eq 49, Scheme I-15) is faster than the decomposition of $Me_3SnR^{-\cdot}$. The reaction of 2-bromoheptane with Me_3SnNa is only slightly inhibited by DNB and DBNO, and it was suggested that few radicals diffuse out of the solvent cage.[105] Kuivila's results[103] show that most of the radical formed in the reaction of 2-bromooctane could be trapped by DCPH. The different inhibitory effect by DNB and DBNO on the reaction of 6-bromo-1-heptenes and 2-bromoheptane is difficult to rationalize since both substrates are secondary bromides. Ashby also found that the reaction of 2-bromooctane proceeds with a high degree of inversion, and suggested that the $Me_3Sn\cdot$ radical attacks the backside of its geminate radical anion ($R\cdot X^-$) in the solvent cage.[105] Kuivila's trapping experiments, however, suggest that the cage reaction is not important since the cage radical would not be trapped by DCPH. The above



Scheme I-15. Possible Mechanisms for the Stannylation of VI

discussion indicates that radical intermediates are involved in the reaction of 2-bromooctane (secondary bromides) with Me_3SnM, however the exact nature of the reaction sequence is still not clear. Contrary to an earlier claim,[108] the results of cyclizable probe studies suggest that an ET mechanism is also involved, at least in part, in the reaction of primary alkyl halides.[109]

The reaction of optically active secondary iodides with organocopper reagents (Ph_2CuLi, Et_2CuLi, $Et_2CuCNLi_2$) gives racemic products whereas the reaction of the corresponding bromides gives products with complete inversion.[110] The reaction of 2-octyl iodide with $LiCuMe_2$ in THF is completely inhibited by DNB for at least 11 minutes, and an $S_{RN}1$ mechanism was suggested for the reaction of the secondary iodides.[111]

The substitution reactions of optically active 2-halooctanes with a series of nucleophiles (LiSPh, LiSPr-*i*, LiCN, $LiPPh_2$, and LAH) proceed with 75.8-100% inversion.[112] It was suggested that partial inversion can occur by an ET sequence.[112] In all the reactions studied, however, the extent of the ET reactions (versus S_N2) has not be quantitatively estimated. and it is too early to draw any conclusions concerning the stereochemistry of ET reactions.

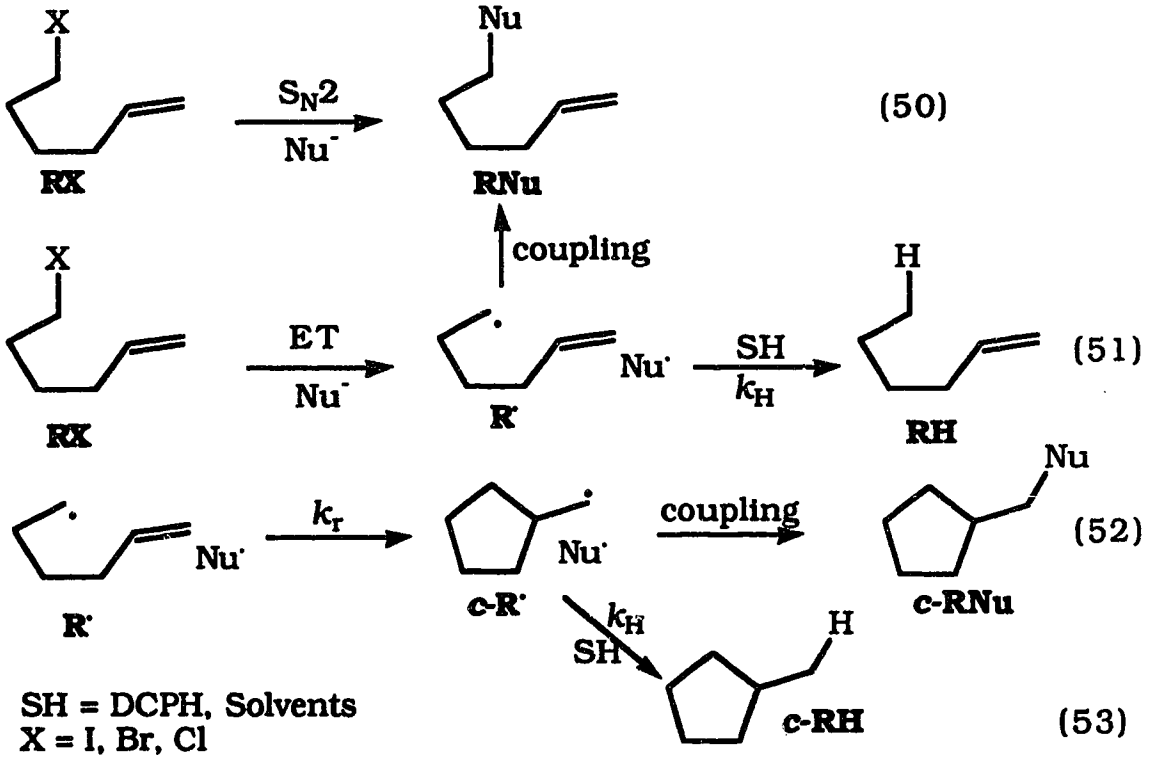
B. Radical Rearrangement Probes

Radicals can undergo various rearrangement reactions. In this section we will only discuss radical cyclization and ring opening

reactions. The rate constants of some important radical rearrangements used in the probe studies are listed in Table I-1.[113]

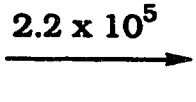
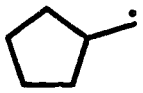
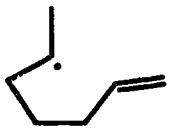
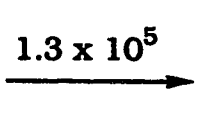
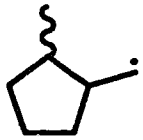
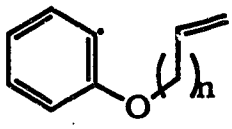
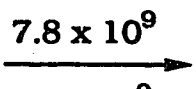
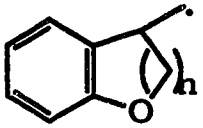
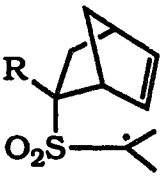
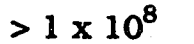
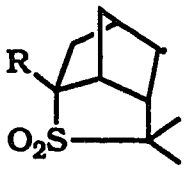
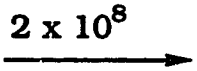
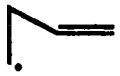
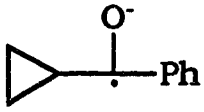
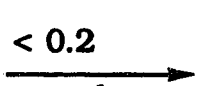
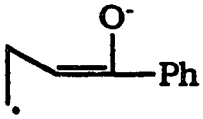
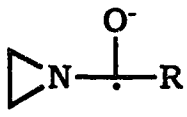
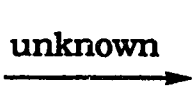
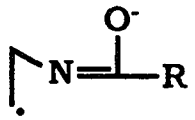
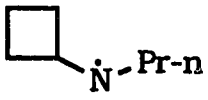
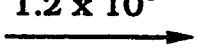
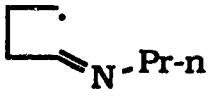
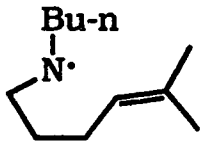
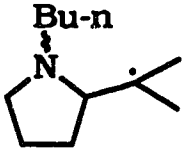
In the cyclizable probe reaction the radical formed upon the ET reaction between the probe and a reagent undergoes a typical radical cyclization to give a cyclized radical. This cyclized radical reacts further to give cyclized products. If the cyclized products cannot be formed by ionic pathways, the formation of these cyclized products can then be used as evidence for the involvement of a radical intermediate (and thus an ET mechanism).

Alkenyl halides, mainly 6-halo-1-hexenes, 6-halo-1-heptenes and their analogues, have been extensively used as mechanistic probes for the ET reactions of alkyl halides with nucleophiles (Scheme I-16).[114]

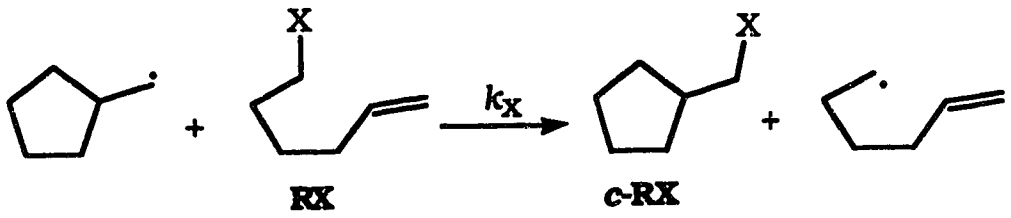


Scheme I-16. Alkenyl Halides as Cyclizable Probes

Table I-1. Radical Rearrangement Reactions Used in the Probe Studies

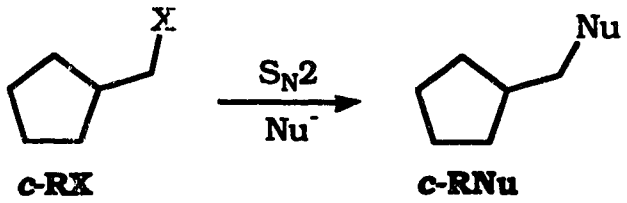
a-j	VIIa-j	k (s^{-1})	VIIIa-j	T (°C), ref.
a		2.2×10^5 		25, 113c
b		1.3×10^5 		25, 113c
c-d	 n = 1, 2	7.8×10^9  3.6×10^9		50, 121
e	 R = CN, Ph	$> 1 \times 10^8$ 		> 65, 124-5
f		2×10^8 		25, 126
g		< 0.2 see the text 		25, 130
h		unknown 		25, 132-3
i		1.2×10^5 		25, 134
j		3.3×10^3		50, 135

Scheme I-16 summarizes possible reactions encountered in the probe studies of the reaction of 5-hexenyl halides (RX) with nucleophiles (Nu^-). The 5-hexenyl radical (R·), formed through an ET between the probe and Nu^-, can cyclize to give the cyclopentylmethyl radical (*c*-R·) or abstract a hydrogen atom from the solvent or a radical trap (such as DCPH) to give 1-hexene (RH). The R· radical can also couple with Nu^- or the radical (Nu·) derived from Nu^- to yield an uncyclized substitution product (RNu). The cyclopentylmethyl radical can undergo hydrogen abstraction to form methylcyclopentane (*c*-RH) or coupling with Nu· or Nu^- to form a cyclized substitution product (*c*-RNu). The formation of these cyclized products (*c*-RH and *c*-RNu) is then used to support the involvement of the ET between the 5-hexenyl halides and the nucleophile in the formation of 5-hexenyl radical. If the halogen abstraction from the starting probe (RX) by the cyclopentylmethyl radical to give the cyclized halide (*c*-RX) and a new 5-hexenyl radical (eq 54) is faster than the other competing reactions of thecyclopentylmethyl radical, the starting probe can be converted



(54)

to the cyclopentylmethyl halides (*c*-RX) by a free radical chain sequence (cyclization and halogen abstraction). An S_N2 reaction of the cyclized halide with Nu^- would also give the cyclized substitution product (*c*-RNu) (eq 55). This reaction sequence (eq 54-55) therefore



(55)

complicates the mechanistic argument that *c*-RNu is formed by an ET mechanism (eq 51-52). Newcomb and Curran[115] first pointed out the possibility of a rapid isomerization of the alkenyl iodide probes through a free radical chain iodine atom transfer sequence in the alkenyl iodide probe studies. The rate constants of the hydrogen and halogen abstraction reaction have been measured for several alkyl radicals[116] so that the reactions shown in Scheme I-16 and eq 54 can be analyzed quantitatively. Such kinetic analyses have been carried out in detail for the reduction of alkenyl halides by metal hydrides.[107,117]

The hydrogen abstraction by alkyl radicals from the solvents (THF) and the main group metal hydrides (LAH and $NaBH_4$) is too slow to compete with the radical cyclization and iodine atom abstraction reactions. Although alkyl radicals can be trapped by DCPH, the resulting DCP· radical is capable of abstracting an iodine from the alkenyl iodide probe and starting a chain sequence (eq 56-59).[118] It was proposed that the cyclized product is formed from the S_N2 reduction of the cyclized alkyl iodide (formed by a iodine transfer chain isomerization).[107] Assuming that the chain reaction is initiated by an ET reaction from metal hydrides to the probe, the estimated

maximum percentage of ET reactions was less than 1% of the total reaction.[107]

$$R^{\cdot} + DCPH \longrightarrow RH + DCP^{\cdot} \quad (56)$$

$$DCP^{\cdot} + RI \longrightarrow DCPI + R^{\cdot} \quad (57)$$

$$R^{\cdot} \longrightarrow c\text{-}R^{\cdot} \quad (58)$$

$$c\text{-}R^{\cdot} + DCPH \longrightarrow c\text{-}RH + DCP^{\cdot} \quad (59)$$

The substitution products (RNu and *c*-RNu) in principle may also be formed by an $S_{RN}1$ reaction (eq 60-61). Experimentally, the $S_{RN}1$

$$R^{\cdot} + Nu^{-} \longrightarrow RNu^{-\cdot} \quad (60)$$

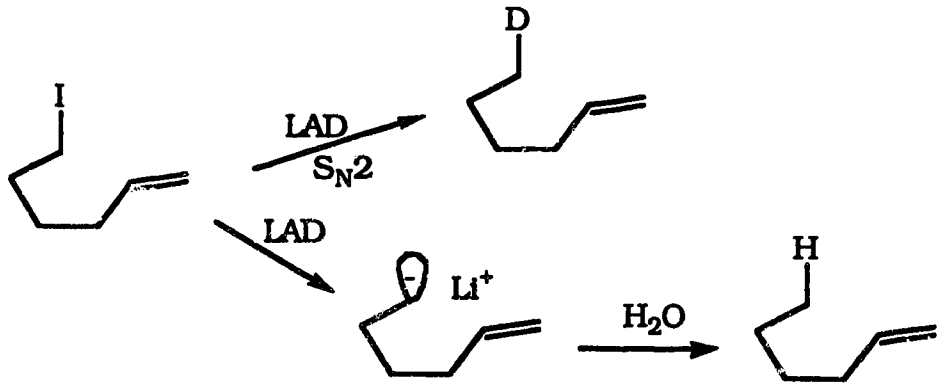
$$RNu^{-\cdot} + RX \longrightarrow RNu + R^{\cdot} + X^{-} \quad (61)$$

mechanism has been established for the reaction of alkylmercuryl halides with a variety of nucleophiles,[12] the reaction of neopentyl halides with several nucleophiles,[24c] and the reaction of *t*-butyl chloride with PPh_2^{-}.[24b] Free radical chain mechanisms such as the one proposed for the LAH reduction of *gem*-dihalocyclopropanes (Scheme I-9) are possible for metal hydride reduction of alkenyl halides. A free radical chain mechanism has been proposed for the reduction of alkyl halides by transition metal hydrides.[119]

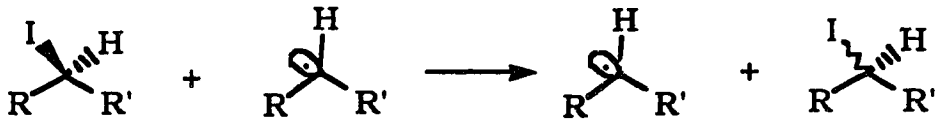
The main argument made by Ashby[114] to support ET mechanisms for the reduction of alkenyl bromides and iodides by metal hydrides is

the formation of reduction products (cyclized and uncyclized).[114] When the reaction of alkenyl iodides was carried out with fully deuterated metal hydrides such as LAD, the reduction products are not 100% monodeuterated.[114] The origin of the undeuterated products is the subject of controversy. Ashby proposed that they are formed by hydrogen abstraction of alkyl radicals from the solvents. Newcomb suggested that the metal hydrides Ashby used are not 100% deuterated.[107]

Another complication with use of the alkenyl halide probe is the possible formation of a carbanion and a carbene intermediate when the reagent is a strong base such as lithium diisopropylamide.[120] If in the reduction of alkenyl iodides by LAD, the S_N2 reaction is the major pathway (eq 62), and if a carbanion intermediate is also formed as a minor pathway and quenched by H_2O to give the undeuterated reduction product (eq 63), then the observed reduction product is not fully deuterated. This proposal provides a reconciliation of the controversy between Ashby and Newcomb on the origin of the undeuterated products.



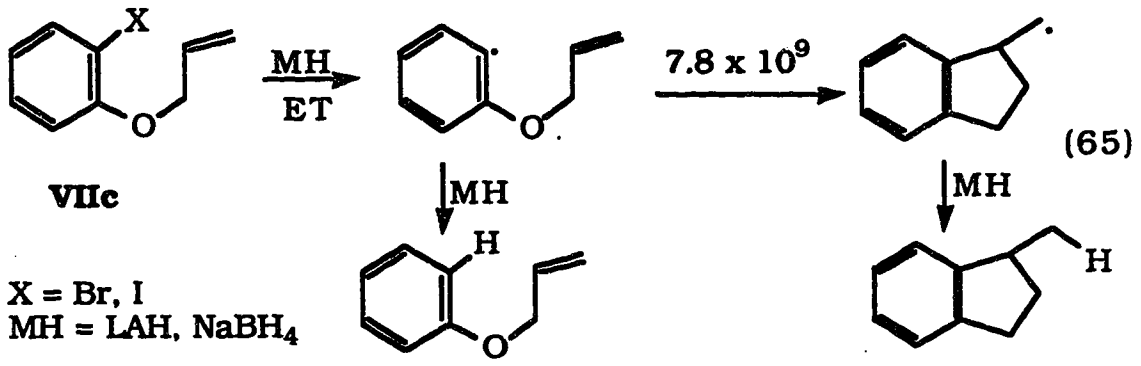
Due to the complications mentioned above, the use of the alkenyl halide probes in the study of ET reactions should be limited only to those cases where the probe isomerization can be excluded or minimized. Since the chlorine or bromine atom abstraction by alkyl radicals is slower than the radical cyclizations, alkenyl chlorides and bromides are better mechanistic probes than alkenyl iodides. Results obtained previously from alkenyl halides should be reexamined with respect to the possible halogen transfer isomerization of the starting alkenyl halides. It should be pointed out here that the iodine transfer reaction also complicates the stereochemical results obtained from optically active alkyl iodides. The starting iodides can be racemized by a rapid iodine transfer chain isomerization sequence (eq 64).[116] This



(64)

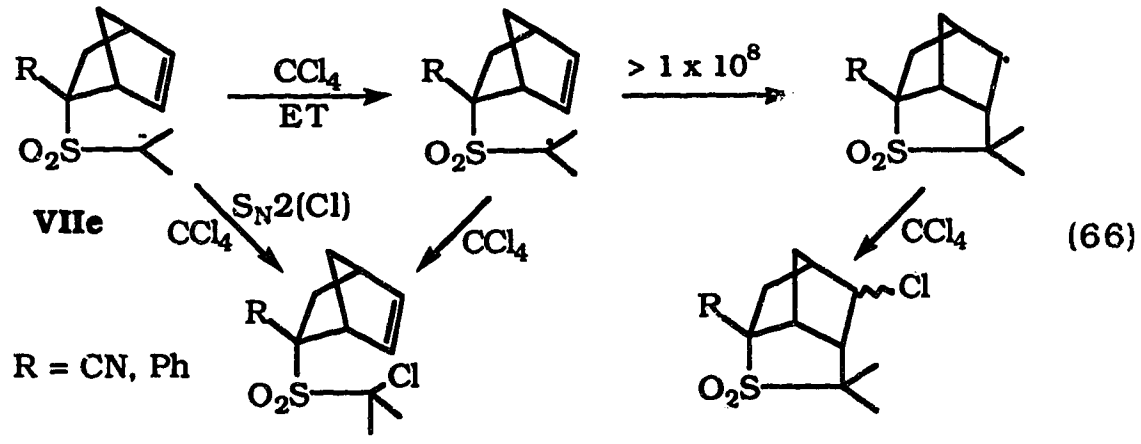
complication can be easily checked by measuring the optical purity of the recovered alkyl halides.

More recently several new radical cyclization reactions with rates much faster than the cyclization of the 5-hexenyl radical have been developed. The cyclizations of O-(prop-2-enyloxy)phenyl radical (**VIIc**) and O-(but-3-enyloxy)phenyl radical (**VIId**) (Table I-1)[121] have been used to study the reaction mechanisms of the reduction of aryl halides by LAH[80] and $NaBH_4$ (eq 65)[122] and the mechanism of the reaction



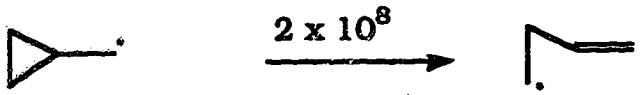
(65)

of aryldiazonium ions with PhS⁻Na⁺.[123] The cyclization of the α-sulfonyl alkyl radical **VIIe** (R = CN, $k > 10^8$ s^1, 65 °C)[124] has been used as an ET probe reaction for the halogenation of sulfones by carbon tetrachloride (eq 66). Since no radical cyclization products are observed in the chlorination reaction, the reaction was proposed to proceed by a direct nucleophilic attack of the carbanion on chlorine ($S_N2(Cl)$). The cyclization of the radical **VIIe** (R = Ph) is even faster ($k = 1.1 \times 10^9$ s^{-1}, 80 °C)[125] than that of the radical **VIIe** (R= CN).



(66)

Another type of radical rearrangement probe employs the ring opening reaction of the cyclopropylcarbinyl radical and its analogues. The cyclopropylcarbinyl radical (**VIIf**) rearranges rapidly to give an allylcarbinyl radical (eq 67) (k = 2.1 x 10^8 s^{-1}, 25 °C),[126] and has



(67)

VIIf

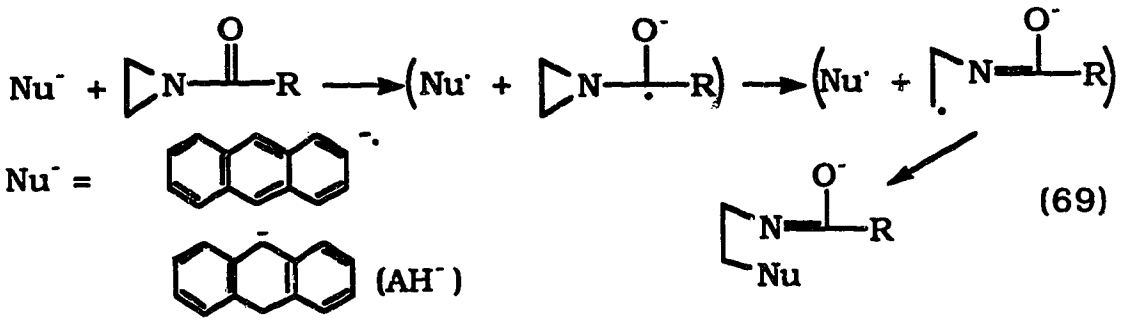
been used as a probe reaction for ET pathways.[127] Since the cyclopropyl ring opening could also proceed via a cationic and an anionic intermediate, or by a process involving no free intermediates,[128] the observation of the ring opened products can not be used as conclusive evidence for the involvement of the cyclopropylcarbinyl radical intermediate.

Cyclopropyl ketones have been used to study the ET reactions of ketones. It was assumed that the cyclopropyl ketyl formed would rearrange as rapidly as the parent cyclopropylcarbinyl radical. In most of these tests no rearrangement products were observed.[129] The rearrangement for the phenyl cyclopropyl ketyl (**VIIg**) was first suggested to be very slow,[130] but was later reported to be reversible (eq 68).[131] Therefore phenyl cyclopropyl ketone is not a good probe

(68)

VIIg

for the ET reactions of ketones. A nitrogen analogue of the cyclopropyl ketyl probe, i.e. the *N*-acyl or *N*-benzoylaziridine ketyl (**VIIh**), has been proposed as an intermediate in the reactions of *N*-acyl or *N*-benzoylaziridines with sodium naphthalenide[132] and anthracene hydride anion (AH^-) (eq 69).[133]



(69)

The rearrangement probes discussed so far are used to detect the formation of radical intermediates from the substrate. Only a few studies reported the use of rearrangement probes in the study of the radical intermediates derived from the reagent. The ring opening of the *N*-cyclobutylpropanaminyl radical (**VIIi**) (k = 1.2 x 10^5 s^{-1}, 25 °C)[134] and the cyclization of the *N*-butyl-5-methyl-4-hexenaminyl radical (**VIIj**) (k = 3.3 x 10^3 s^{-1}, 50 °C)[135] were used to detect the formation of aminyl radical intermediates in the reaction of lithium dialkylamides with a variety of reagents. Ring opened products or cyclization products were observed in the reaction of *N*-lithio-*N*-propylcyclobutylamine or *N*-lithio-*N*-butyl-5-methyl-4-hexenamine with strong oxidants such as (*E*)-2-*tert*-butyl-3-phenyloxaziridine and thianthrene radical cation, but no such radical-derived products were detected in the reaction with weak oxidants such as aryl ketones,

pyridine, and methyl iodide. It was proposed that ET processes are not important in the reaction of lithium dialkylamide with these substrates.[135]

C. Fragmentation Probes

An organic compound upon accepting or donating an electron may undergo a rapid fragmentation to give an organic radical and an anion or a cation irreversibly. If the products derived from the radical or the ion (anion or cation) can not be obtained by polar ionic pathways, the reacting organic compound may be classified as a fragmentation probe. This type of probe has not been studied as systematically as the cyclizable probe but it has great potential both in mechanistic and synthetic studies.

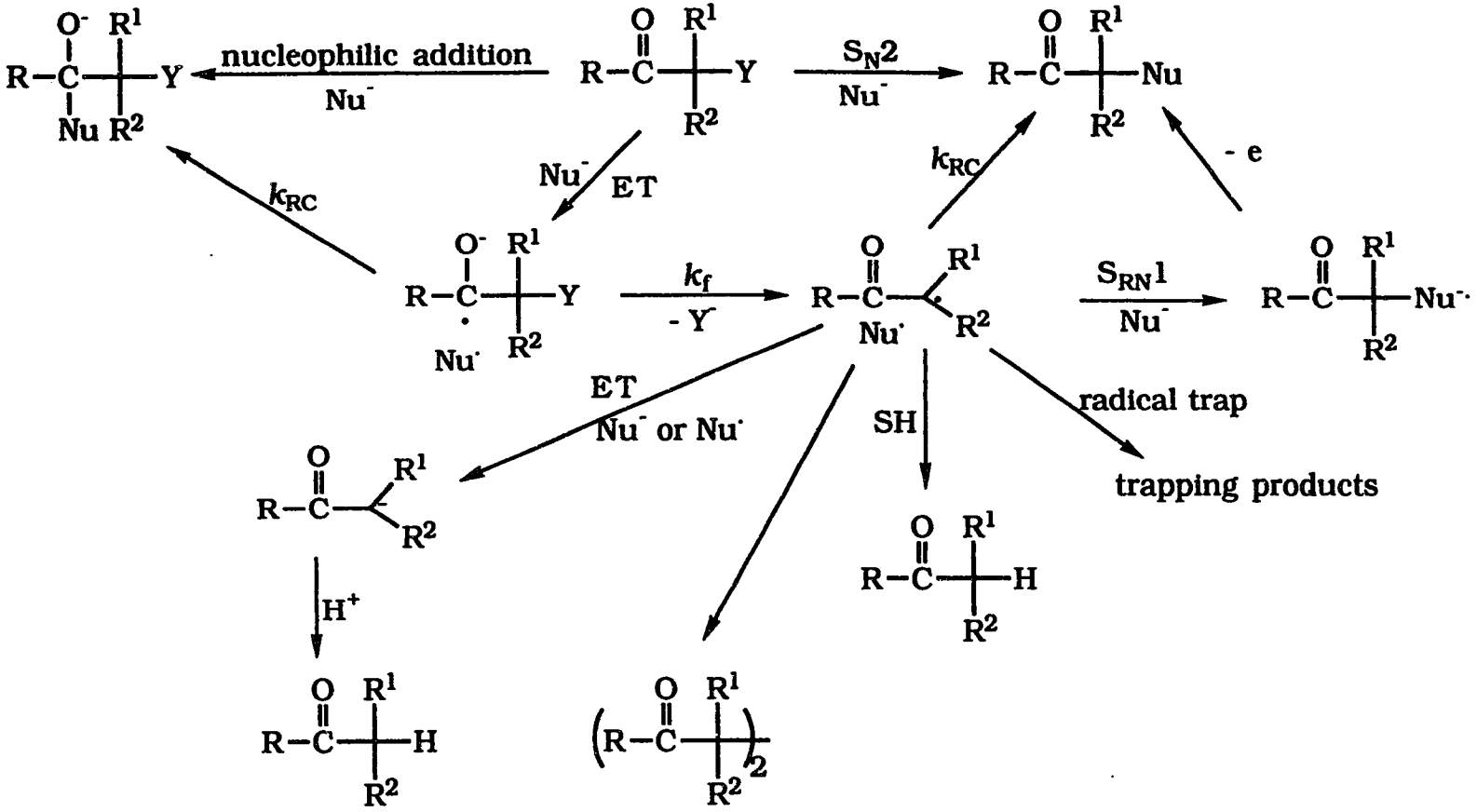
Most of the fragmentation probes have been designed to detect radical anion formation. In the last few years, however, there have been an increasing number of reports dealing with the radical cation cleavage reactions, especially the cleavage reactions of the carbon-carbon single bond.[136] Based on these radical cation cleavage reactions, chemical probes can be designed to study ET reactions in many electrophilic (and oxidation) reactions. Such probes have been developed to study enzymatic oxidations and used as mechanism-based inhibitors.[137]

Various organic substrates (RX) participating in the $S_{RN}1$ reactions are examples of fragmentation probes. These substrates are normally unreactive towards nucleophiles due to the poor leaving ability of X

and/or steric crowding at the reaction center. Upon accepting an electron to form the radical anion, the substrate cleaves readily to give a radical (R·) and an anion (X^-). The subsequent reaction of the radical with a nucleophile (Nu^-) is not subjected to severe steric retardation. A variety of leaving groups such as Cl, Br, NO_2, N_3, HgX, SO_2Ar, SR, OPh, OCOR, and CMe_2NO_2 have been found to participate in $S_{RN}1$ reactions.[16] The cleavage rate of the radical anions can be measured by electrochemical techniques, pulse radiolysis and flash photolysis. For very fast cleavage reactions special techniques are needed. At present there are only a few reports of the measured fragmentation rates for $S_{RN}1$ substrates in aliphatic systems.[138] The rate constants for the reaction of radicals with Nu^- are even more difficult to measure, and only a few relative rates have been reported.[139]

Another major class of the fragmentation probe involves ketones with a suitable leaving group (Y) located at the α- or vinylogous γ position. Upon accepting an electron from the donor (Nu^-) to form a ketyl, the ketone fragmentation probe cleaves rapidly to give an enolyl radical and an anion (Y^-), see Scheme I-17.

The observation of products derived from the enolyl radical provides strong evidence for ET reactions. The formation of α-substitution or 1,2-addition products provides no definitive information concerning the reaction mechanism (ET or polar ionic). The 1,2-addition product may be produced by a direct nucleophilic addition, or by an ET reaction followed by fast coupling of the radical ion pair. The substitution products can be produced by a direct nucleophilic substitution or by an $S_{RN}1$ mechanism (Scheme I-17).



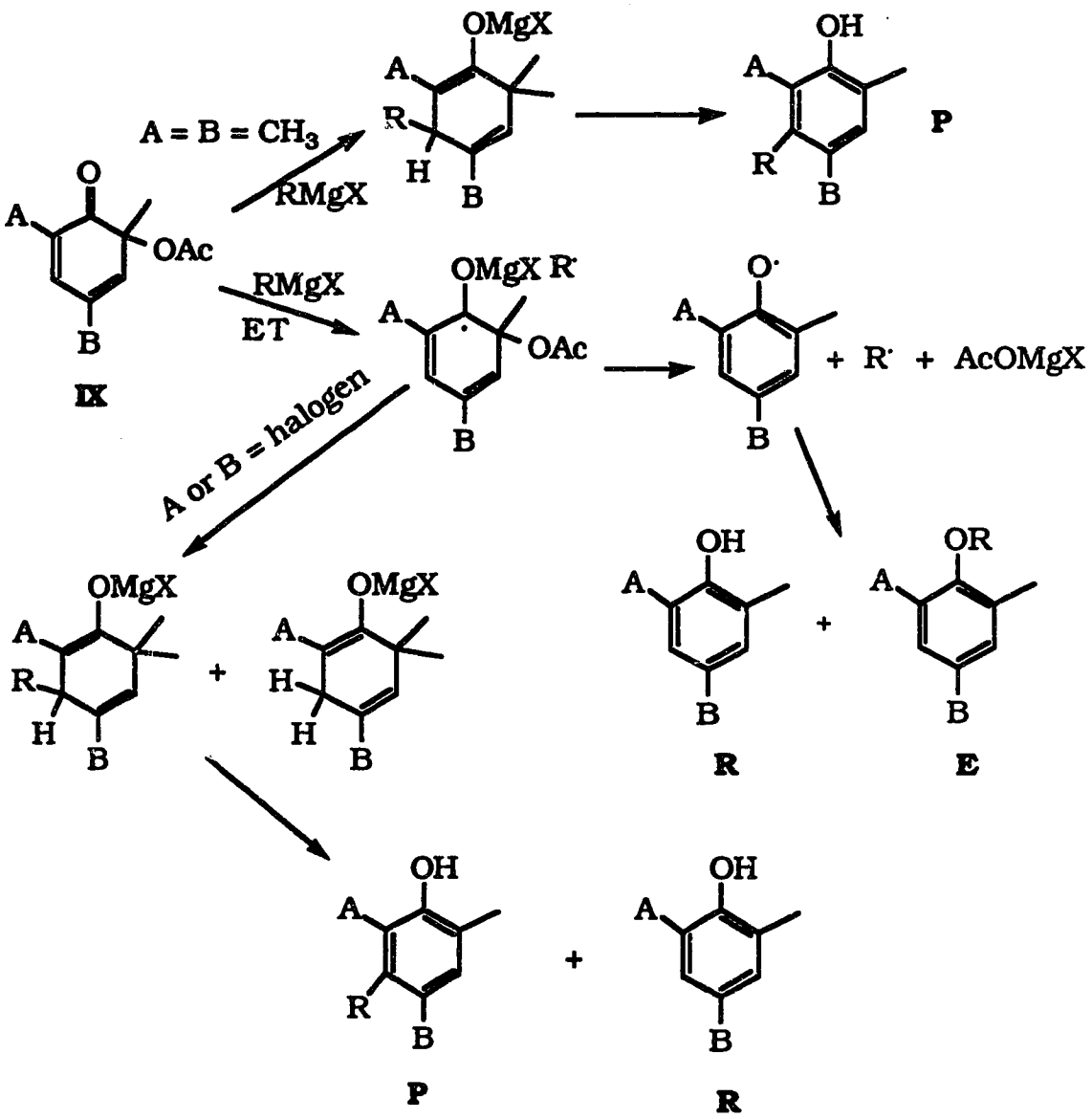
Scheme I-17. Possible Mechanisms for the Reaction of α-Substituted Ketones with Nucleophiles

The electrochemical reduction of an α-substituted ketone shows that the ketyl cleaves readily to give an enolyl radical for a variety of α-substituents[140] (i.e. X (halogen), OPh,[142] SR,[143] SO_2R,[144] and SOR[145]). The rate constants for these cleavage reactions, however, are still unknown.

α-Haloketones have been studied as probes for ET reactions. Russell[146] proposed an $S_{RN}1$ mechanism for the reaction of *p*-nitro or *p*-cyanophenacyl chloride with the anion of 2-nitropropane. An ET chain sequence was also suggested for the reaction of 2,2-diphenyl-2-halo-*N*,*N*-dimethylacetamide with sodium methoxide.[147] Tanner[148] has extensively studied the ET hydrogen atom abstraction chain reduction of α-haloacetophenones with a variety of reagents (tin hydrides, silanes, BNAH, and NADH). The formation of acetophenone can be inhibited by DNB and initiated by AIBN. The radical inhibitor and initiator have no effect on the formation of α-halohydrin. These results suggest that acetophenone is formed by an ET chain sequence, whereas the α-halohydrin is formed by a direct hydride transfer (see Section I-3 for details).

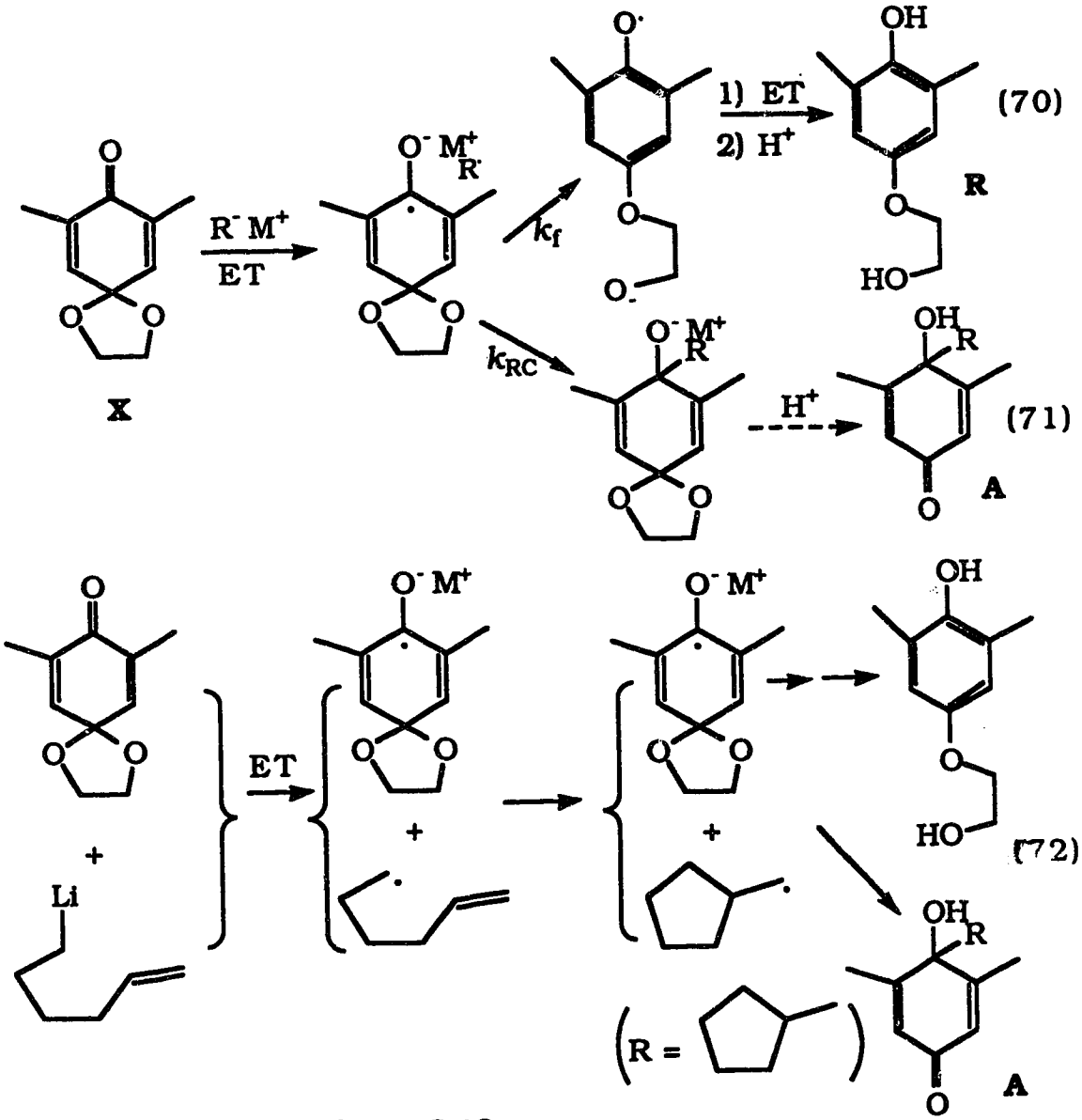
In addition to these ET chain reactions of α-haloketones, there are several other reports of the ET reactions of α-substituted ketones. The argument for an ET mechanism is largely based on product studies. Miller studied the reaction of *o*-quinol acetates (6-acetoxy-2,4-cyclohexa-2,4-dien-1-ones) (**IX**) with Grignard reagents.[149] The reaction of **IX** with aryl or primary alkyl Grignard reagents gives *m*-arylated or alkylated phenols (P). The major product in the reaction with secondary, tertiary, and benzylic Grignard reagents are alkyl aryl

ethers (E) and reduction products (R). Products E and R are formed by the ET sequence, whereas product P is formed by a direct 1,4-addition or an ET sequence, see Scheme I-18.



Scheme I-18

Liotta suggested the use of 4,4-(ethylenedioxy)-2,6-dimethyl-2,5-cyclohexadienone (**X**) as a chemical probe for ET reactions.[150] The reaction of the probe with alkyl organolithium reagents, alkyl Grignard reagents and alkyl organocopper compounds gives both the reduction product (R) and addition product (A) (eq 70-71, Scheme I-19). The

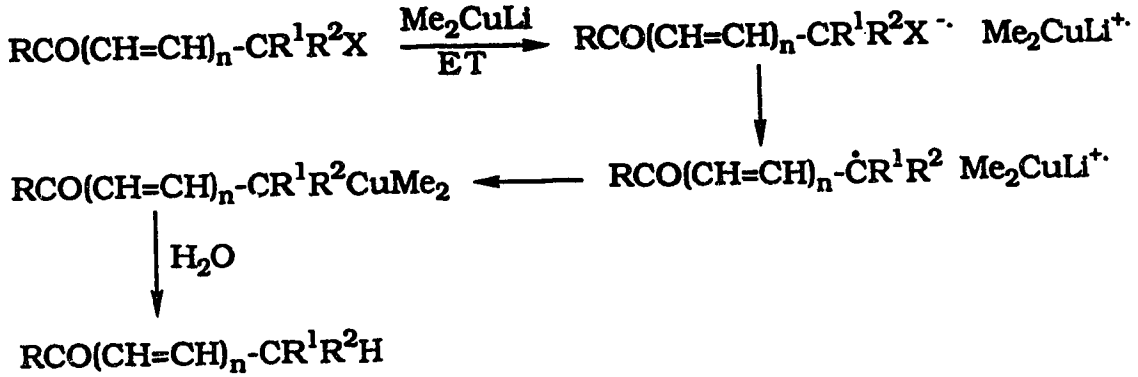


Scheme I-19

reduction product is formed by an ET sequence (eq 70), whereas the addition product can be formed by an ET sequence (eq 71) or by a direct nucleophilic addition reaction. In the reaction of **X** with 1-lithio-5-hexene, the addition product (A) was found to contain only the cyclopentylcarbinyl fragment (eq 72, Scheme I-19). This observation was used to suggest that all products (addition and reduction) are derived from ET reactions (Scheme I-19). The ketyl cleavage (k_f) must be slow enough to allow the cyclization of the 5-hexenyl radical to yield the cyclopentylcarbinyl radical. The cyclized radical couples with the ketyl to give the cyclized addition product. These two processes compete efficiently with the ketyl cleavage reaction.

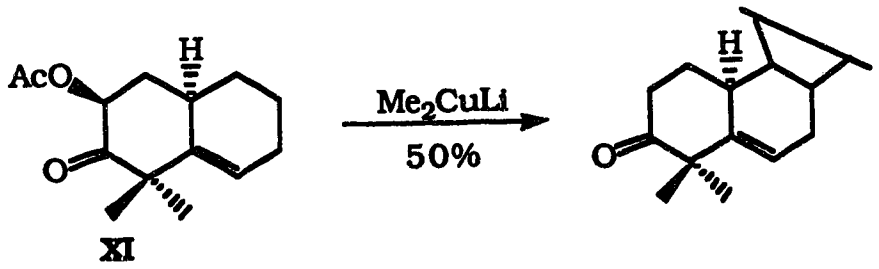
Imamoto employed Liotta's probe to study the mechanism of the reaction of Grignard reagents with ketones in the presence of cerium chloride.[151] Surprisingly, the presence of the Lewis acid cerium chloride has no appreciable effect on the product distribution (reduction versus addition). An ET mechanism was suggested for the cerium chloride promoted Grignard reaction. The reaction of α-bromoacetophenone with a vinyl Grignard reagent in the presence of cerium chloride gives the normal addition product in high yield (95%). Studies of the reaction of α-bromoacetophenone with other Grignard reagents would help to establish the relationship between the structure of the Grignard reagent and its ET reactivity. The reaction of Liotta's probe with aryl or vinyl Grignard reagents can provide similar information.

There have been scattered reports of the use of ketone fragmentation probes to study ET reactions of Me_2CuLi. The main evidence cited for the ET pathway is the formation of the reduction product. The possible ET sequence for the formation of the reduction product is shown in Scheme I-20. The key step is the ketyl



Scheme I-20

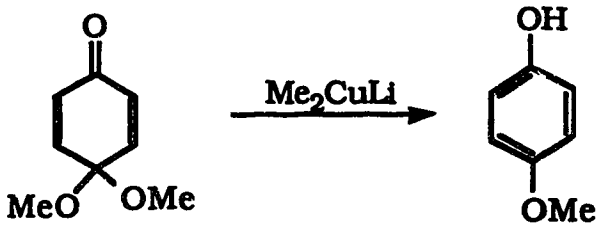
fragmentation. 2-Bromocyclododecanone reacts with Me_2CuLi to give cyclododecanone through the enolate intermediate.[152] Bull[153] found that several α-epoxy, α-acetoxy, and α-bromoketones such as **XI** react with Me_2CuLi to yield the reduction products (eq 73), and suggested



XI

(73)

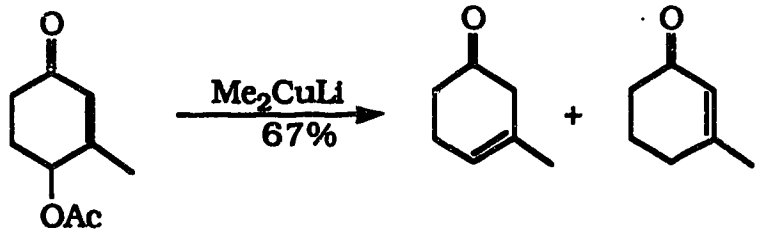
an ET pathway for these reactions. 4,4-Dimethoxycyclohexadienone (**XII**) was reported to yield 4-methoxyphenol (eq 74) by an ET



(74)

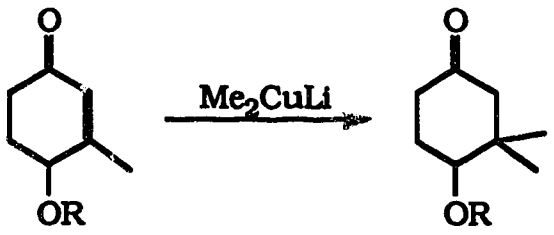
XII

mechanism.[154] 4-Acetoxycyclohexenone-2 (**XIII**) gives cyclohexenone-2 (eq 75) but 4-alkoxycyclohexenone-2 yields only the conjugate addition product, 4-alkoxy-3-methylcyclohexanone (eq 76). The formation of the conjugated addition product is due to the slower cleavage of 4-alkoxide as compared to 4-acetate.[155] Similarly,



(75)

XIII



(76)

α-bromo and α-acetoxyisobutyrophenones (**XIV**) (eq 77) give the reduction product, whereas α-methoxyisobutyrophenone (**XV**) mainly gives the addition product (eq 78).[130] γ-Ketolactones undergo similar

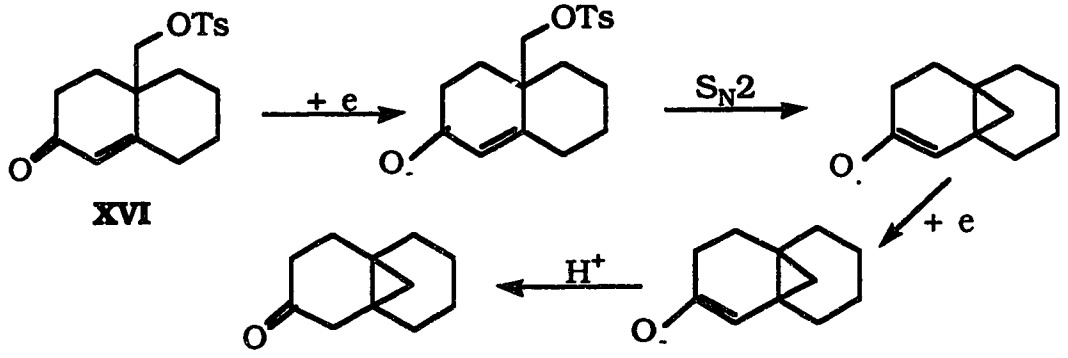
$$\underset{\textbf{XIV}}{PhCOCMe_2OAc} \xrightarrow{Me_2CuLi} \underset{54\%}{PhCOCHMe_2} + \underset{8\%}{PhCH(OH)CHMe_2} \qquad (77)$$

$$\underset{\textbf{XV}}{PhCOCMe_2OMe} \xrightarrow{Me_2CuLi} \underset{0.1\%}{PhCOCHMe_2} + \underset{58\%}{PhCMe(OH)CMe_2OMe} \qquad (78)$$

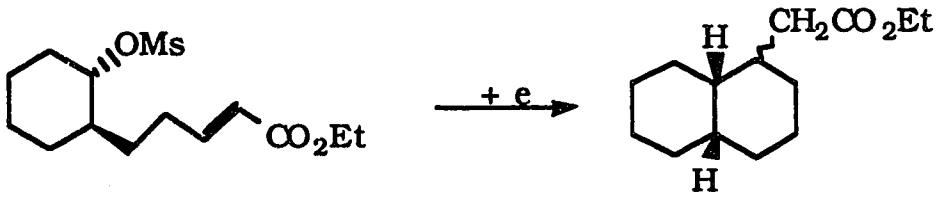
ET reductions.[156] A series of γ-acetoxy-α,β-enoates were reported to react with organocuprates to give the copper enolates.[157] Although no mechanisms were proposed, the ET sequence suggested for the other ketone fragmentation probes seems likely in this system. Finally the reduction of selenium salts by Grignard reagents has also been proposed to proceed by an ET pathway.[158]

In all the reactions discussed above the copper enolate was assumed to be the intermediate leading to the reduction product since it could be trapped by electrophiles other than water such as methyl iodide and acetic anhydride. The enolate is presumably formed by a second electron transfer from the cuprate to the enolyl radical.[152-157] It has been, however, suggested that the enolate could also be formed by a one-step oxidative addition reaction.[159] In order to differentiate between the ET and the oxidative addition pathways inter or intramolecular traps for the enolyl radical should be employed to establish the radical intermediacy.

In another type of the ketone fragmentation probe, the ketyl anion formed undergoes a rapid intramolecular S_N2 reaction with a leaving group suitably located in the probe to form a cyclized product. One such probe is 10-hydroxymethyl-$\Delta^{1,9}$-2-octalone tosylate (**XVI**). The ketyl formed upon an ET to **XVI** undergoes intramolecular substitution to give the cyclopropyl carbinyl radical which accepts another electron to form the enolate anion (Scheme I-21). Stereochemical studies of the electrochemical reduction of unsaturated esters such as **XVII** and **XVIII** (eq 79-80) have established the reaction sequence shown in



Scheme I-21



(79)

XVII

No Reaction (80)

XVIII

Scheme I-21.[160] The reductive cyclization of 10-hydroxy-methyl-$\Delta^{1,9}$-2-octalone tosylate (**XVI**) can also be accomplished by electrochemical reduction[161] and dissolving metal reduction.[162] **XVI** and its analogues have been used as probes for ET reactions with organocuprates (e.g. eq 59, Scheme I-14).[163]

Although the reductive dehalogenation of α-haloketones by metal carbonyls has been reported, the detailed mechanism is still not cle . Radical intermediacy has been proposed to explain the formation of dimeric (1,4-diketones) and reduction products (formed by hydrogen abstraction from solvents). A radical mechanism was proposed for the reduction of α-acetoxy and α-haloketones by $Fe(CO)_5$ to explain the hydrogen abstraction from the added toluene.[164] In other cases, the dehalogenated ketone is formed through the protonation of an enolate intermediate.[165] Other metal carbonyls that have been studied to effect the dehalogenation are iron-graphite,[166] $HFe(CO)_4^-$,[167] $Mo(CO)_6$,[168] $Mo(CO)_5SiMe_3$,[169] and $Co(CO)_4^-$.[170]

Reagents such as zinc[171] and SmI_2[172] have been used to reduce α-substituted ketones to the corresponding ketones through an ET sequence. The reductive dehalogenation of α-haloketones has been accomplished with a variety of reagents.[173] Although no mechanistic studies have been carried out, most of these reactions are assumed to proceed via the nucleophilic attack at the α-halogen to give the enolate ions.

In summary ketone fragmentation probes have been used to detect ET reactions with organocuprates and Grignard reagents, but no systematic study has been carried out with these probes. The

fragmentation probes are used mainly for the reaction of ketones and the cyclizable probes are used for the reaction of alkyl or aryl halides. Unlike cyclizable probes, studies with these fragmentation probes are only qualitative since no kinetic data are available to allow for a detailed analysis of the reaction mechanism. Future research should be directed at more quantitative studies with these probes.

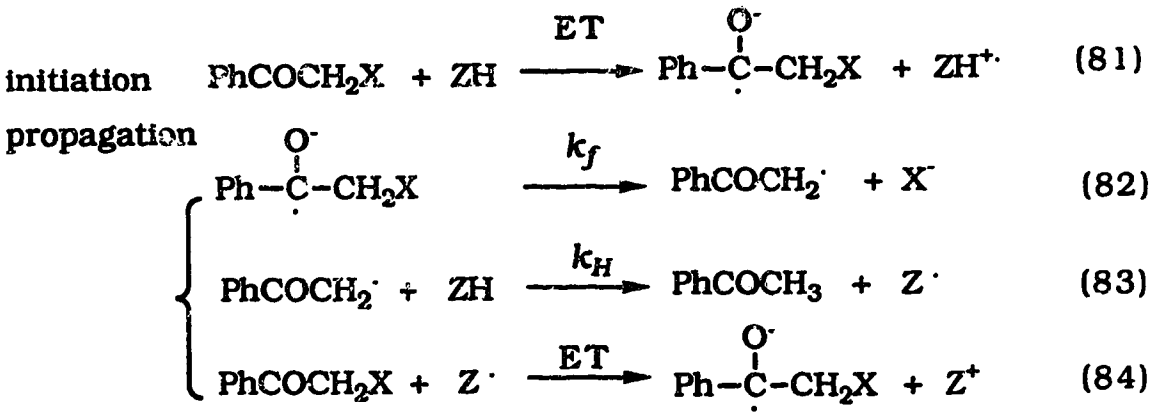
D. Conclusions

In the previous sections we have reviewed the use of chemical probes in studying ET reactions in organic chemistry. Although radical intermediates can be detected by EPR spectroscopy, chemical probes provide more direct evidence for the involvement of radical intermediates in the reaction pathway. If the radical-derived products are obtained from two diamagnetic species in high yield, it may be concluded that the reaction mainly proceeds via an ET sequence.[174] Another advantage of using a chemical probe is the possibility of analyzing the reaction kinetics quantitatively from the known rate constants of the secondary radical reactions. Time-resolved spectroscopic techniques such as EPR spectroscopy,[175] CIDNP effect,[176] flash photolysis, and pulse radiolysis have been used to measure the radical reaction rate constants and these absolute rate constants can then be used as a basis for the quantitative analysis of the ET reactions of chemical probes. In the future the use of chemical probes to study reaction products should be combined with detailed kinetic studies by electrochemical and laser spectroscopic methods.

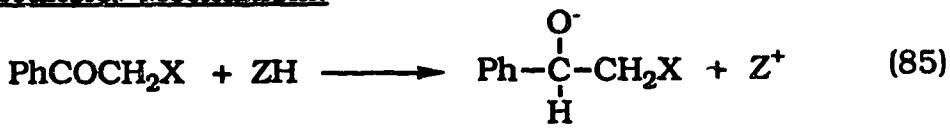
I-3. Research Proposals

α-Haloacetophenones have been used as ketone fragmentation probes to differentiate between ET and hydride transfer mechanisms for the reductions of ketones by several hydride donors (Scheme I-22).[148] Acetophenone is the product of an ET chain process (eq 81-84). The chain process can be initiated by the ET between the α-haloacetophenone and the hydride donor (ZH, eq 81). The chain

A. Electron Transfer Hydrogen Abstraction Chain Mechanism:



B. Hydride Transfer Mechanism:



X = Br, Cl, F

ZH = R_3SnH, R_3SiH, BNAH, NADH, DMBI

Scheme I-22. Mechanisms for the Reduction of α-Haloacetophenones

propagation sequence involves ketyl fragmentation (eq 82), hydrogen atom transfer (eq 83), and electron transfer (eq 84). The formation of acetophenone is subject to radical chain initiation and inhibition. The α-halohydrin ($PhCHOHCH_2X$) is the product of a hydride transfer process (eq 85). Product, radical chain initiation, and radical chain inhibition studies can be used to differentiate between the ET and hydride processes.

The tin hydride reduction of α-fluoroacetophenone gives acetophenone and α-fluorohydrin.[148a] When the solvent is changed from benzene to methanol, the yield of the fluorohydrin increases whereas the yield of acetophenone is not affected significantly. The formation of acetophenone is inhibited by DNB and initiated by AIBN. These results suggest that acetophenone is formed by an ET chain process (eq 81-84, Scheme I-22) and the fluorohydrin is formed by a hydride transfer process (eq 85, Scheme I-22). Similar competing ET and hydride transfer processes were observed in the tin hydride reduction of α-chloroacetophenone[148b] and in the fluoride ion catalyzed silane reduction of α-fluoroacetophenone.[148c]

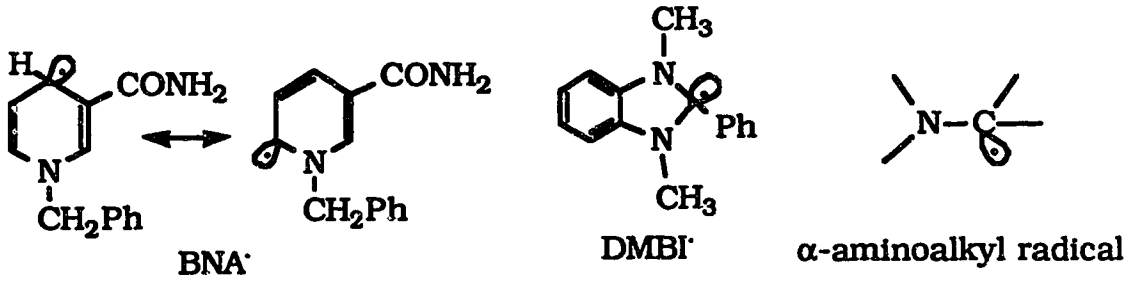
N-Benzyl-1,4-dihydronicotinamide (BNAH) and its analogues have been extensively investigated as model compounds for the NADH coenzymes. Several mechanistic pathways including ET processes have been suggested for the formal hydride transfer from BNAH to carbonyl compounds.[177] Tanner used α-haloacetophenones as chemical probes to study the reaction mechanism of the reduction of ketones by BNAH.[148d] The mechanistic pathways can be distinguished on the basis of the products formed since acetophenone is the product of an

ET chain sequence (eq 81-84, Scheme I-22) and the halohydrin is the product of a hydride transfer sequence (eq 85, Scheme I-22). 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 ET chain inhibitor, DNB. These results are consistent with the ET chain mechanism (eq 81-84, Scheme I-22). The coenzyme NADH itself can reduce α-bromoacetophenone in aqueous solution to give acetophenone by a similar ET chain sequence. The enzyme (HLADH)-mediated NADH reduction of α-haloketones only produces the optically pure α-halohydrins. It was concluded that the enzymatic reduction most likely proceeds by a direct hydride transfer mechanism.[148e]

1,3-Dimethyl-2-phenylbenzimidazoline (DMBI) was used as a selective reducing agent for α-halocarbonyl compouds[178] and α,β-unsaturated carbonyl compounds.[179] The authors proposed a direct S_N2 hydride transfer mechanism for the dehalogenation reaction of the α-halocarbonyl compounds based on both steric and electronic arguments. The order of reactivities was found to be Br > Cl > F, and the rate of the reduction was found to be primary > secondary > tertiary (for substitution at the halogenated carbon). Since DMBI is a better ET reagent than BNAH in the ET chain reduction of α-nitro-sulfones,[180] and the reduction products of α-haloketones by DMBI are identical with those by BNAH,[148d] the previously proposed mechanism for the reduction by DMBI was reexamined in detail.[181] Free radical chain initiators and inhibitors were used to establish a possible free

radical chain sequence, and trapping experiments were carried out to substantiate the free radical intermediate. The results of these studies are discussed in Chapter 2.

Our results show that the reduction of α-haloketones by DMBI proceeds by the same sequence as the reduction by BNAH (eq 81-84, Scheme I-22, ZH = DMBI). According to the ET chain mechanism the intermediate BNAH and DMBI radicals (BNA· and DMBI·) transfer an electron to the α-haloketone (eq 84, Scheme I-22). Structurally BNA· and DMBI· can be considered as α-aminoalkyl radicals. It is of interest



to investigate the possibility that other α-aminoalkyl radicals derived from simple tertiary amines can undergo similar ET reactions. To test this possibilty we carried out the reaction of α-haloketones with *N,N*-dimethylaniline (DMA) and triethylamine (TEA) in the presence of radical initiators. The preliminary results of this study are reported in Chapter 3.

As discussed in the section on fragmentation probes (I-2.C), substrates with a variety of leaving groups (Y) other than halogens such as NO_2, N_3, HgX, SO_2Ar, SAr, OAr, and OCOR can participate in the

$S_{RN}1$ reaction,[16] but the previous studies of ketone fragmentation probes only used X (halogen), OCOR, and OR as the leaving group. It is of interest to investigate whether those leaving groups which can participate in the $S_{RN}1$ reaction could be used in the ketone fragmentation probes (Y = NO_2, N_3, HgX, SO_2Ar, SAr, OAr, and OCOR, Scheme I-10). From our work on the ET reaction of α-halo-acetophenones with DMBI, it is natural to select the reaction of α-substituted acetophenones ($PhCOCH_2Y$, Y = OCOR, OPh, SO_2Ar, and SPh) with DMBI as a model to study the ET reactions of α-substituted acetophenones. For comparison, the reaction with triphenyltin hydride was also investigated. The results of these studies are described in Chapter 4.

The results of the reduction of these α-substituted acetophenones with DMBI are encouraging. The α-substituted acetophenones we have studied undergo the same ET chain reduction with DMBI as α-halo-acetophenones to give acetophenone. As expected, these substrates show different reactivities towards DMBI. The rate constants of the cleavage reaction of the ketyls of these α-substituted acetophenones have not been measured previously so that a quantitative analysis of the reaction kinetics in the probe studies with these ketones is impossible. Although the rate constants for these cleavage reactions can be determined by advanced electrochemical and laser spectroscopic methods, we developed a simple chemical method to estimate the cleavage rate constants of α-substituted acetophenone ketyls by using the intramolecular competitive reduction of α-substituted and ring-halogenated acetophenones ($XC_6H_4COCH_2Y$, X =

I, Br, Cl; Y = Br, Cl, F, OCOPh, $OCOCH_3$, and OPh). During these studies we also designed new chemical probes for ET reactions of substituted benzophenones and enones. The results are discussed in Chapter 5.

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CHAPTER 2

On the Mechanism of the Reduction of α-Haloketones by 1,3-Dimethyl-2-phenylbenzimidazoline. Reduction by an ET Hydrogen Atom Abstraction Mechanism

1. A version of this chapter has been published. Tanner, D.D.; Chen, J.J. *J. Org. Chem.* **1989**, *54*, 3842.

Introduction

The reduction of carbonyl compounds is one of the most fundamental reactions in organic chemistry. Despite its wide synthetic applications, the mechanistic details for most of these reductions are still not clearly delineated. The reduction may conceivably proceed by either a homolytic or heterolytic pathway. In recent years considerable attention has been given to the proposal that an electron transfer (ET) step is involved in a number of organic reactions that were previously considered to proceed by a polar mechanism.[1] A variety of chemically based probes have been used to differentiate polar and ET pathways (see Chapter 1). α-Haloacetophenones have been used successfully as probes to differentiate between these two pathways (Scheme II-1) in the reduction by organotin hydrides,[2] organosilanes,[3] *N*-benzyl-1,4-dihydronicotinamide (BNAH) and its analogues,[4] and in the enzyme (HLADH) mediated reductions by NADH.[5] Acetophenone is the product of the ET process (eq 1-4, Scheme II-1) and the halohydrin is the product of the hydride transfer process (eq 5, Scheme II-1). It is of some importance to extend this probe to other reduction systems in order to gather more information about the elementary steps involved, see Scheme II-1.

It was reported that 1,3-dimethyl-2-phenylbenzimidazoline (DMBI) could selectively reduce a series of α-halocarbonyl compounds to their corresponding aldehydes or ketones without affecting the carbonyl group.[6] Using both steric and electronic arguments a direct hydride transfer (S_N2) mechanism was proposed as an explanation of the

A. Electron Transfer Hydrogen Abstraction Chain Mechanism:

initiation $PhCOCH_2X + ZH \xrightarrow{ET} Ph-\dot{C}(O^-)-CH_2X + ZH^{+\cdot}$ (1)

propagation

$Ph-\dot{C}(O^-)-CH_2X \xrightarrow{k_f} PhCOCH_2\cdot + X^-$ (2)

$PhCOCH_2\cdot + ZH \xrightarrow{k_H} PhCOCH_3 + Z\cdot$ (3)

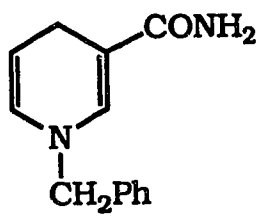
$PhCOCH_2X + Z\cdot \xrightarrow{ET} Ph-\dot{C}(O^-)-CH_2X + Z^+$ (4)

B. Hydride Transfer Mechanism:

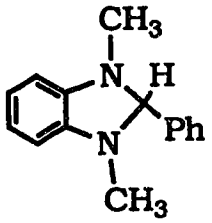
$PhCOCH_2X + ZH \longrightarrow Ph-C(O^-)(H)-CH_2X + Z^+$ (5)

X = Br, Cl, F

ZH = R_3SnH, R_3SiH, BNAH, NADH, DMBI



BNAH



DMBI

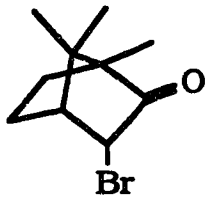
Scheme II-1. Mechanisms for the Reduction of α-Haloacetophenones

experimental results. The order of reactivities was found to be Br > Cl > F, and qualitatively the rates of reduction were found to be primary > secondary > tertiary (for substitution at the halogenated carbon). These structure-reactivity relationships reported are equally consistent with the alternative ET hydrogen atom abstraction process proposed for the reductions by BNAH. Since the reagent, DMBI, is structurally analogous to BNAH, and the reduction products of α-halo-ketones by DMBI are identical to those by BNAH,[4] the previously proposed mechanism for the DMBI reductions was re-examined in more detail.

Results and Discussion

α-Haloacetophenones (**Ia-c**), α-halopropiophenones (**IIa-c**), α-halo-isobutyrophenones (**IIIa-b**), α-bromocamphor (**IV**) and ethyl 2-bromo-propionate (**V**) were chosen as model compounds to study the mechanism of the DMBI reduction of α-halocarbonyl compounds. The

$PhCOCH_2X$	$PhCOCHCH_3X$	$PhCOC(CH_3)_2X$
Ia-c	**IIa-c**	**IIIa-c**
a, X = Br	a, X = Br	a, X = Br
b, X = Cl	b, X = Cl	b, X = Cl
c, X = F	c, X = F	c, X = SPh



IV

$CH_3CHBrCO_2C_2H_5$

V

reductions were carried out in several solvents (C_6H_6, THF, MeOH). Radical initiation (AIBN, or di-*tert*-butylperoxyoxalate, DBPO) and inhibition (dinitrobenzenes, *p*-DNB or *m*-DNB) were used to establish whether a free radical chain reduction sequence was involved. The reaction yields were deliberately not optimized so that the initiation and inhibition could be easily observed. The results of these studies are listed in Table II-1 to Table II-4.

Table II-1. The Reduction of α-Haloacetophenones (Ia-c) by DMBI

Reaction	**Ia-c**	Conditions [a]	Additive	Yield (%) $PhCOCH_3$
1	**Ia**	C_6H_6, 61 °C, 0.4 h	-	29.1
2			*m*-DNB (2%)	0.8
3		C_6H_6, 23 °C, 2 h	-	33.6
4			*m*-DNB (2%)	1.4
5			DBPO (5%) [b]	99.5
6		C_6H_6, 61 °C, 4 h [c]	-	1.1
7			AIBN (6%)	78.9
8	**Ib**	C_6H_6, 61 °C, 20 h	-	29
9			AIBN (5%)	99
10			*m*-DNB (4%)	0.0
11		THF, 61 °C, 5 h	-	55
12			AIBN (4%)	78
13			*m*-DNB (5%)	0.0
14	**Ic**	THF, 61 °C, 53 h	-	1.9
15			AIBN (5%)	77.9
16		MeOH, 61 °C, 64 h	-	15.2
17			AIBN (5%)	89.1
18			*p*-DNB (5%)	10.1 [d]

[a] **[Ia-c]**/[DMBI] = 0.1 M/0.1 M. [b] Rapid reaction took place when the reagents were mixed. [c] DMBI (0.01 M) and $PhCOCH_2Br$ (0.01 M). [d] 1.8% of $PhCHOHCH_2F$ was also observed. In all other cases no $PhCHOHCH_2X$ was detected by GC and GC-IR.

Table II-2. The Reduction of α-Halopropiophenones (IIa-c) by DMBI [a]

Reaction	IIa-c	Times	Additive	Yield (%) $PhCOCH_2CH_3$
19	**IIa**	48 h	-	45.2
20			AIBN (4%)	101
21			*p*-DNB (5%)	8.8
22	**IIb**	73 h	-	46.3
23			AIBN (6%)	85.6
24			*p*-DNB (6%)	1.4
25	**IIc**	51h	-	3.0
26			AIBN (8%)	29.1

[a] All reactions were run in THF at 61 °C. [**IIa-c**]/[DMBI] = 0.1 M/0.1 M.

Table II-3. The Reduction of α-Haloisobutyrophenones (IIIa-b) by DMBI[a]

Reaction	IIIa-b	Time	Additive	Yield (%) $PhCOCHMe_2$	IIIa-b
27	**IIIa**	96 h	-	5.4	89.6
28			AIBN (4%)	11.4	79.7
29	**IIIb**	77 h	-	4.7	84.8
30			AIBN (3%)	14.8	81.7

[a] All reactions were run in THF at 61 °C.
[**IIIa-b**]/[DMBI] = 0.1 M/0.1 M.

Table II-4. The Reduction of IV and V by DMBI

Reaction	Substrate	Conditions	Additive	Yield (%)
31	**IV**	THF, 61 °C, 48 h	-	1.4
32			AIBN (7%)	47.6
33		THF, 90 °C, 72 h	-	26.8
34			*p*-DNB (4%)	2.2
35	**V**	THF, 21 °C, 9 h	-	73.3
36			*m*-DNB (5%)	0.0

1. Free Radical Chain Reduction

Examination of the results obtained from the reduction of α-bromoacetophenone (**Ia**) by DMBI in benzene (Table II-1, reactions 1-2) at 61 °C establishes that the reduction proceeds via a free radical chain mechanism. Very small amounts of DNB could inhibit the chain reaction. In order to observe radical chain initiation, the reduction was also carried out at room temperature for a longer period using the low temperature initiator, DBPO.[7] With DBPO, a reaction that could be inhibited took place upon the mixing of the reagents, and solid $DMBI^+Br^-$ precipitated from the solution (Table II-1, reactions 3-5). At a lower concentration the bimolecular ET induced initiation (vide infra) was not effective even at 61 °C (Table II-1, reaction 6), but the reaction could be initiated with AIBN (Table II-1, reactions 7). Similar

inhibition and initiation were observed in the reduction of α-chloro and α-fluoroacetophenone (**Ib** and **Ic**, see Table II-1). These results indicate that the α-haloacetophenones (**Ia-c**) are reduced via the same mechanism. Qualitatively, the reactivity follows the order **Ia** > **Ib** > **Ic** obtained previously for the reductions by organotin hydrides[2] and BNAH.[4]

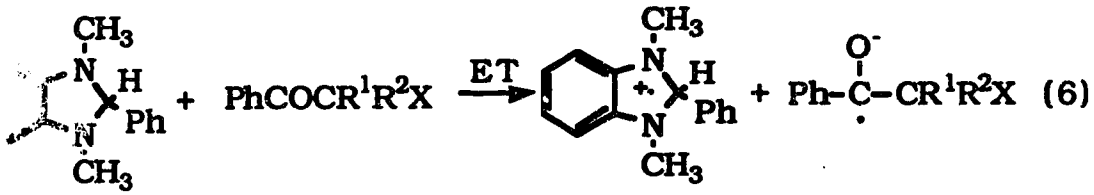
The effect of solvent polarity was briefly studied for the reduction of **Ic**. In the more polar protic solvent, methanol, the thermal initiation becomes more facile, but more importantly, the hydride transfer product ($PhCHOHCH_2F$) was detected for the reaction run with added DNB (Table II-1, reaction 18). In the polar solvents, when the rapid radical chain is inhibited, the slower hydride transfer reaction becomes competitive.

The DMBI reductions of α-halopropiophenones (**IIa-c**, Table II-2), α-bromocamphor (**IV**) and ethyl 2-bromopropionate (**V**) (Table II-4) appear to proceed by the same free radical chain mechanism since both initiation by AIBN and inhibition by DNB were also observed. The reduction of α-haloisobutyrophenones (**IIIa-b**, Table II-3), however, showed only slight initiation and no inhibition was observed. Nevertheless, it is difficult to rationalize that the reduction of the tertiary halides would proceed via an S_N2 direct hydride transfer mechanism while primary and secondary halides are reduced by a free radical chain mechanism.

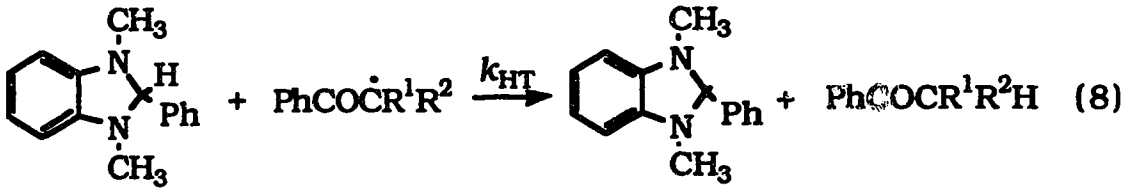
The detailed mechanism, similar to the general scheme for the reduction of α-haloacetophenones by a hydride donor ZH (Scheme II-1), is proposed for the reduction by DMBI (Scheme II-2). Results

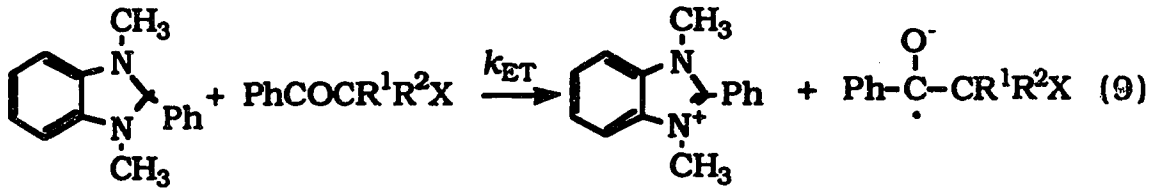
discussed in the following sections provide convincing evidence for this mechanistic sequence.

initiation



propagation





Scheme II-2. The ET Hydrogen Abstraction Chain Mechanism for the Reduction of α-Haloketones by DMBI

2. Competitive Reactivity Study

Since both steric and electronic effects have been used to argue for the S_N2 hydride transfer mechanism,[6] a series of relative rate constants were measured for substrates (**I-III**) whose reactions have different steric demands. The results are listed in Table II-5.

Table II-5. The Relative Reactivities of $PhCOCR^1R^1X$ towards DMBI[a]

X	Ia-c	IIa-c	IIIa-b
Br	1	0.78	0.40
Cl	1	0.78	0.20
F	1	0.40	

[a] The relative rate constants of **II** and **III** to **I** within the same halogen series. There is no relationship between different halogens in the table.

The primary, secondary, and tertiary reactivities of the α-halo-ketones appear to be the same within a factor of two for each series of halogens. Within a series, the largest difference between a primary and a tertiary halide is 5 : 1. This value is rather small for an S_N2 reaction involving the sterically hindered DMBI, since, for the S_N2 reactions of **Ib** and **IIIb** with I^-, the difference between primary and tertiary chloride is reported to be 330000.[8] However, the magnitude of the difference is that which could be expected for a sterically less demanding ET chain reaction (eq 6-9, Scheme II-2).

The competitive rates of reduction between the series of different halogens could not be measured directly, since during the competitive reductions the starting α-haloketones were found to undergo halogen exchange. In order to ascertain the origin of the halogen exchange, several control experiments were carried out and the results are listed in Table II-6. By inspecting the results shown in Table II-6 (reactions 38-41), it is clear that the halide ions formed in the DMBI reduction of α-haloketones are responsible for the halogen exchange. The halide ions produced in the DMBI reduction of α-haloketones undergo S_N2 reactions with the starting α-haloketones resulting in the isomerization of the α-haloketones (eq 10).[9]

$$PhCOCHRX + Y^- \rightleftharpoons PhCOCHRY + X^- \qquad (10)$$

R = H, Me
X = Cl, Br
Y = Cl, Br

Qualitatively the same order reported previously (Br > Cl > F)[2-4] can be recognized for the rates of the reactions of the series of primary and secondary haloketones (see Tables II-1 and II-2). This order, which was attributed to the leaving ability of the halogen,[6] can also be correlated to the ability of the substrate to accept an electron (i.e. its electron affinity).[2]

Table II-6. The Halogen Exchange in the $PhCOCH_2Cl$ (Ib)/ $PhCOCHCH_3Br$ (IIa), 1/1 Mixture

Reaction	Conditions [a]	Additive	Products (%)			
			Ib	**IIb** [b]	**Ia** [c]	**IIa**
37	56 h	-	98.0	-	-	101.7
38	*56 h*	*AIBN (12%)*	*90.3*	*6.5*	*10.8*	*97.0*
39	56 h	$Et_4N^+Br^-$ (10%), $Me_4N^+Cl^-$ (20%)	50.0	58.6	45.8	49.8
40	8 h	DMBI (9%)	44.9	50.6	31.8	31.2
41	8 h	$DMBI^+Br^-$ (10%)	49.7	55.5	35.7	40.1

[a] All reactions were carried out in THF at 61 °C in the dark. **[Ib]** = **[IIa]** = 0.1 M. [b] The yield was calculated based on $PhCOCHCH_3Br$ used. [c] The yield was calculated based on $PhCOCH_2Cl$ used.

In the competitive experiments the reduction of α-bromoacetophenone or α-chloroacetophenone appeared to be inhibited when it was carried out in the presence of α-bromo or α-chloroisobutyrophenone. The reductions of several pairs of α-haloketones were examined as a function of time. The results are displayed in Figs. II-1 to II-3.

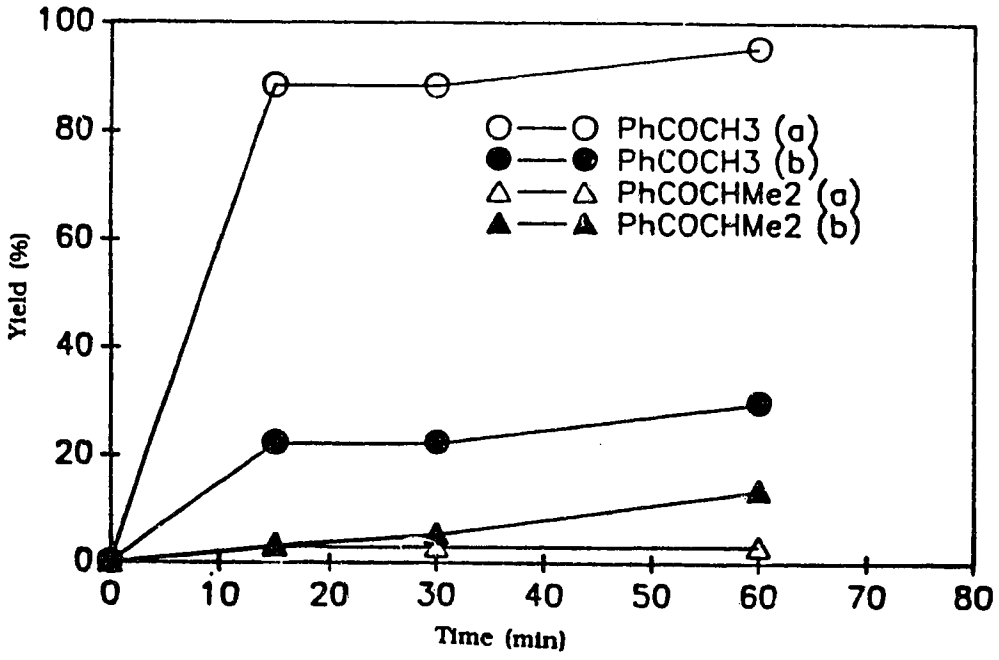


Fig. II-1. The reduction of **Ia** and **IIIa** by DMBI in THF at 61 °C (yield vs. reaction time). [**Ia**] = [**IIIa**] = [DMBI] = 0.03 M. (a) reactions of a single substrate; (b) competitive reactions.

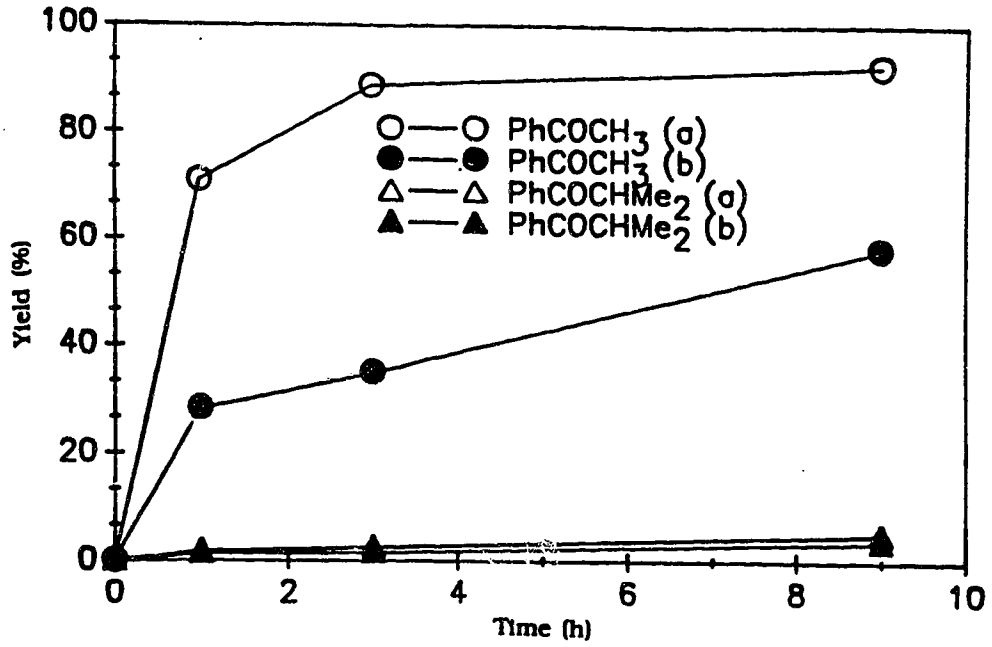


Fig. II-2. The reduction of **Ib** and **IIIb** by DMBI in THF at 61 °C (yield vs. reaction time). [**Ib**] = [**IIIb**] = [DMBI] = 0.03 M. (a) reactions of a single substrate; (b) competitive reactions.

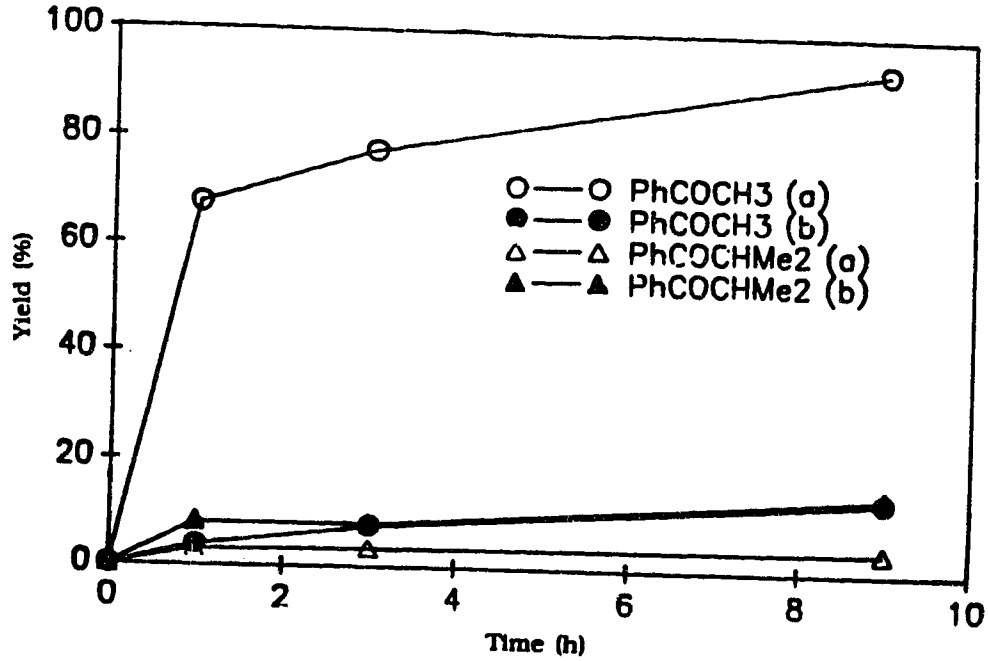


Fig. II-3. The reduction of **Ib** and **IIIa** by DMBI in THF at 61 °C (yield vs. reaction time). [**Ib**] = [**IIIa**] = [DMBI] = 0.03 M. (a) reactions of a single substrate; (b) competitive reactions.

It is clear from Fig. II-1 that the reduction of α-bromoacetophenone (**Ia**) by DMBI is inhibited by the addition of an equivalent of α-bromoisobutyrophenone (**IIIa**). The tertiary haloketone itself was not appreciably reduced during these competitive reductions (see Fig. II-1). The same behaviour was observed when α-chloroacetophenone was reduced in the presence of α-chloroisobutyrophenone (**IIIb**) (Fig. II-2). These observations are not in agreement with the one-step direct hydride transfer mechanism previously proposed.[6] If the reduction of the α-haloketones by DMBI did proceed by the S_N2 mechanism, the reduction of the more reactive primary haloketones **Ia-b** would not be affected by the presence of the less reactive tertiary haloketones **IIa-b**. Since the reduction of the primary and secondary halides is shown to proceed via a free radical mechanism (vide supra), the reduction of the tertiary halides most likely proceeds via the same mechanism.

The inhibitory effect of the tertiary halides on the reduction of the primary halides could be rationalized by a comparison of the expected differences in the rates of the propagation steps for the chain mechanism (eq 8-9, Scheme II-2). Hydrogen atom transfer would be more favorable for the primary radical than for the analogous tertiary radical ($k_{HT}(1^o) > k_{HT}(3^o)$). The ET from the DMBI radical (Z·) to **Ia** or **IIIa** would not be expected to differ greatly although an ET (eq 9, Scheme II-2) followed by a fast cleavage of the ketyl (eq 7, Scheme II-2) would undoubtedly favor the tertiary halide ($k_{ET}^{IIIa} > k_{ET}^{Ia}$). Such inequalities in rates are required to explain the observed inhibition. The tertiary substrate (**IIIa**) reacts rapidly with DMBI· (eq 9, Scheme

II-2) but does not carry the chain. The primary substrate (**Ia**) would then appear to be unreactive. The effect would be even greater when the tertiary substrate (**IIIa**) is competitively reduced along with the less reactive primary halide **Ib**. The same inequalities will still exist but the differences in ET rates would be amplified even further ($k_{ET}^{IIIa} > k_{ET}^{Ia} > k_{ET}^{Ib}$), see Fig. II-3. The amount of inhibited reduction of **Ib** exhibited during the competitive reductions of **Ib** and **IIIa** must be taken as an upper limit since halogen exchange, bromide for chloride, produces α-bromo-acetophenone (**Ia**) which is reduced to acetophenone about 50 times faster than **Ib**. In consistent with this argument, no **Ia** was detected in the unreacted reaction mixture. It can therefore be suggested that the small amount of acetophenone produced (< 10%) would be even smaller if no **Ia** had been formed by the halogen exchange pathway.

3. Enolyl Radical Addition to 1-Hexene

By carrying out the reductions in 1-hexene, the intermediate enolyl radicals could be trapped for both the primary and secondary radicals produced during the reduction of **Ib** and **IIb** by DMBI, see Scheme II-3. Scheme II-3 also provides the mechanism for the trapping reaction. The intermediate enolyl radical (PhCOCHR·) formed in the ET chain reduction of the α-haloketones with DMBI can either abstract a hydrogen from DMBI to give the reduction product ($PhCOCH_2R$) (eq 11) or add to 1-hexene to produce a new alkyl radical (eq 12). This new radical subsequently abstracts a hydrogen from

Scheme II-3. Trapping of the Intermediate Enolyl Radical by 1-Hexene

Results:

$$PhCOCH_2Cl \xrightarrow[61\ ^{\circ}C,\ 5\%\ AIBN,\ 4\ days]{n\text{-}C_4H_9CH=CH_2,\ DMBI} \underset{27\%}{PhCOCH_3} + \underset{7.6\%}{PhCOCH_2C_6H_{13}\text{-}n}$$

$$PhCOCH(CH_3)Cl \longrightarrow \underset{5.6\%}{PhCOC_2H_5} + \underset{16.6\%}{PhCOCH(CH_3)C_6H_{13}\text{-}n}$$

$$PhCOC(CH_3)_2Cl \longrightarrow \underset{1.4\%}{PhCOCH(CH_3)_2} + \underset{0.0\%}{PhCOC(CH_3)_2C_6H_{13}\text{-}n}$$

Mechanism:

$$PhCOCHRCl + Z^{\cdot} \longrightarrow PhCO\dot{C}HR \xrightarrow{ZH} PhCOCH_2R + Z^{\cdot} \quad (11)$$

$$PhCO\dot{C}HR \xrightarrow{1\text{-hexene}} PhCOCHRCH_2\dot{C}HC_4H_9\text{-}n \quad (12)$$

$$PhCOCHRCH_2\dot{C}HC_4H_9\text{-}n + ZH \longrightarrow PhCOCHRCH_2CH_2C_4H_9\text{-}n + Z^{\cdot} \quad (13)$$

R = CH_3, H; ZH = DMBI

DMBI to yield the trapping product and the DMBI radical (eq 13) which carries the chain reaction. As expected, the trapping reaction of the tertiary radical produced from **IIIb** was unsuccessful since the addition of the stabilized and sterically hindered tertiary enolyl radical ($PhCOCMe_2\cdot$) to olefins is expected to be unfavorable.

In agreement with our trapping results, the enolyl radical ($PhCOCH_2\cdot$) formed from an ET to phenacylmercuryl chloride ($PhCOCH_2HgCl$) was subsequently reported to add to enamines, *N*-methylpyrrole, and norbornene.[10]

4. The Mechanism for the DMBI Reduction of α-Halocarbonyl Compounds

The observation that the reduction of α-halocarbonyl compounds (I-IV) can be initiated (AIBN and DBPO) and inhibited (DNB) and that the reduction of **Ia-b** could be competitively inhibited by **IIIa** established the free radical chain nature of the reduction. The trapping of the intermediate enolyl radical by 1-hexene supports our proposal that the reduction of α-haloketones by DMBI proceeds by a free radical chain mechanism. The possible chain sequence shown in Scheme II-2 includes ET as the initiation and one of the chain propagation steps.

It is not unreasonable to assume that the initiation step in the absence of additives (AIBN or DBPO) involves an ET between α-haloketone and DMBI to give a radical ion pair (eq 6, Scheme II-2). The ease of this ET depends on the electron affinity of the halide. For example, **Ia** undergoes facile reduction while **Ic** requires initiation by AIBN in order to achieve a reasonable yield of reduction product. Since the ET initiation involves a bimolecular reaction between an α-haloketone and DMBI, the efficiency of the initiation should also depend on the concentrations of both the substrate and reagent. Thus, the thermal ET initiation between **Ia** and DMBI is inefficient when the concentrations of both **Ia** and DMBI are reduced by a factor of 10 (see reactions 6 and 7, Table II-1). In support of the proposed ET initiation reaction, the facility of ET from DMBI has been established with several acceptors: 2,4,6-triphenylpyrylium perchlorate and triphenylmethyl chloride.[11a-b] When DMBI was allowed to react in acetonitrile

(AN) with either of these substrates, the corresponding EPR spectra from the 2,4,6-triphenylpyranyl radical or the triphenylmethyl radical were observed.[11a-b] An ET from substituted benzimidazolines to a number of acceptors has been reported to give EPR spectra.[11c]

Because of the structural similarity between DMBI and BNAH, it is of interest to compare the reactivity of the α-haloacetophenones towards these two reagents. **Ia** reacts with DMBI (34%, 2 h) in benzene even at room temperature but is nearly unreactive towards BNAH (10%, 24 h)[4] in AN even at 61 °C. Similarly, **Ic** reacts readily with DMBI in the presence of AIBN in both THF and methanol while it is unreactive towards BNAH in AN.[4] These results could be explained on the basis of the electron donating ability of ZH (DMBI or BNAH) or Z· (DMBI· or BNA·), i.e. the oxidation potentials of ZH and Z·.

The reversible oxidation potential of DMBI was reported to be 0.29 V (SCE) in DMF.[11] We found that DMBI showed two oxidation peaks on a glassy carbon electrode in AN. The first peak, the one electron oxidation of DMBI, was quasi-reversible at a scan rate > 500 mV/s. The oxidation potential obtained in AN (0.31 V, SCE) is very close to that reported in DMF. The oxidation potential of BNAH, on the other hand, is less certain. The electrochemical oxidation of BNAH only showed completely irreversible waves.[12] Several methods have been used to estimate its oxidation potential. The values (0.57-0.89 V, SCE, AN)[13] are invariably much more positive than that of DMBI. The ET from DMBI to the α-haloketones is therefore more favorable than the ET from BNAH (eq 1, Scheme II-1). In accordance with this suggestion, the uninitiated DMBI reduction of **Ia** takes place readily at

room temperture, whereas the uninitiated BNAH reduction of **Ia** is sluggish even at 61 °C.

The oxidation potential of the intermediate radical (DMBI· or BNA·) from DMBI and BNAH can, in principle, be obtained from the electrochemical reduction of the corresponding salt ($DMBI^+$ or BNA^+). The value for BNA· was measured by the electrochemical reduction of BNA^+ (-0.94 V, SCE, AN).[14] The electrochemical reduction of $DMBI^+$ in AN, however, only showed an irreversible two-electron reduction wave even at high scan rates (100 V/s). The peak potential (E^p = -1.75 V, SCE, 500 mV/s) shifted negatively when the scan rate was increased. Since the AIBN initiated reduction of **Ic** by DMBI is much more effective than the reduction by BNAH,[4] it is reasonable to assume that the ET from DMBI· to **Ic** (eq 4, Scheme II-1) is more favorable than the ET from BNA· to **Ic** and, therefore, that the oxidation potential of DMBI· is more negative than that of BNA· (-0.94 V, SCE, AN).

5. The Thiophenol Promoted Free Radical Chain Reduction of α-Haloisobutyrophenones

Since it was assumed that the hydrogen atom transfer between the tertiary radical $PhCOC(CH_3)_2$· and DMBI (eq 9, Scheme II-2) was too inefficient to carry the chain reduction of α-chloro and α-bromo-isobutyrophenone (**IIIa-b**) by DMBI, it was anticipated that the chain reaction would be facilitated by the addition of a chain transfer agent which itself produces a radical that could carry the chain. As

anticipated, the addition of thiophenol increased the yield of the reduction product significantly. The results of the effect of PhSH on the DMBI reduction of **IIIa-b** are summarized in Table II-7.

The reduction of α-bromoisobutyrophenone (**IIIa**) which had been found to be relatively unreactive toward DMBI (reactions 42-4, Table II-7) was significantly accelerated by the addition of thiophenol (reactions 46-51, Table II-7). An optimum yield of the reduction product was obtained when two equivalents of thiophenol were used. In addition to the reduction product, isobutyrophenone, α-phenylthio-isobutyrophenone (**IIIc**) was also produced as a minor product (~1-5%). In the presence of *p*-DNB, the formation of the reduction product was inhibited (reactions 47, 49, 51, Table II-7), but the formation of the substitution product (**IIIc**) cannot be inhibited. In the absence of DMBI, **Ia** was unreactive toward PhSH even in the presence of AIBN (reaction 52, Table II-7).

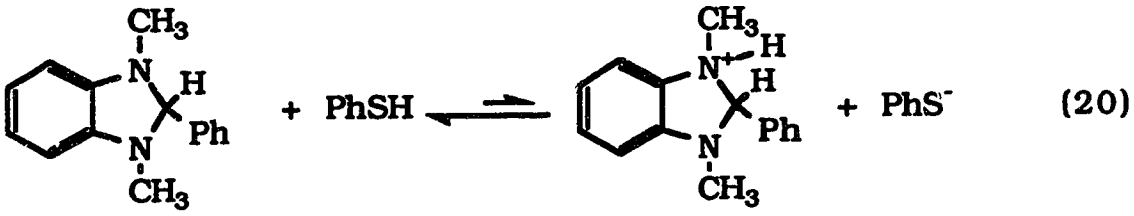
Similarly, the reduction of α-chloroisobutyrophenone (**IIIb**) was enhanced by PhSH (reactions 53-58, Table II-7), albeit the thermal reaction was much slower than that of the bromide **IIIa**. Nevertheless the reduction could be inhibited by DNB (reaction 57, Table II-7) and initiated by AIBN (reaction 58, Table II-7). The yield of the substitution product (**IIIc**) also increased considerably in the presence of DNB (reaction 57, Table II-7).

Since the reduction in the presence of thiophenol could be initiated by AIBN and inhibited by DNB, it is reasonable to assume that it is formed via a free radical chain mechanism (Scheme II-4). The substitution product, on the other hand, is likely formed by a slow

Table II-7. The PhSH Promoted Reduction of $PhCOCMe_2X$ (IIIa-b) by DMBI

Reaction	X	Conditions [a]	$PhCOCHMe_2$	$PhCOCMe_2X$	$PhCOCMe_2SPh$
42	Br	96 h [b]	5.4	89.6	-
43		96 h, 4% AIBN [b]	11.4	79.7	-
44		96 h, 5% *p*-DNB [b]	12.2	79.7	-
45		104 h	19.1	63.4	-
46		104 h, 0.5 eq PhSH	79.5	20.5	4.0
47		104 h, 0.5 eq PhSH, 10% *p*-DNB	0.2	57.0	18.6
48		35 h, 1 eq PhSH	46.9	57.0	4.6
49		35 h, 1 eq PhSH, 10% *p*-DNB	2.2	63.4	35.6
50		20 h, 2 eq PhSH	92.7	-	1.7
51		20 h, 2 eq PhSH, 9% *p*-DNB	0.7	52.0	22.2
52		104 h, 8% AIBN [c]	2.6	92.9	-
53	Cl	77 h [b]	4.7	84.8	-
54		77 h, 3% AIBN [b]	14.8	81.7	-
55		77 h, 3% *p*-DNB [b]	1.0	92.9	-
56		27 h, 2 eq PhSH	14.5	77.8	8.0
57		27 h, 2 eq PhSH, 6% *p*-DNB	0.0	79.9	23.7
58		27 h, 2 eq PhSH, 6.7% AIBN	96.5	-	2.6

[a] All reactions were carried out in THF at 61 °C with **[IIIa-b]** : [DMBI] = 1 : 2 except where specified. **[IIIa-b]** = 0.05 M. [b] $[PhCOCMe_2X]$: [DMBI] =1 : 1. [c] No DMBI was used.



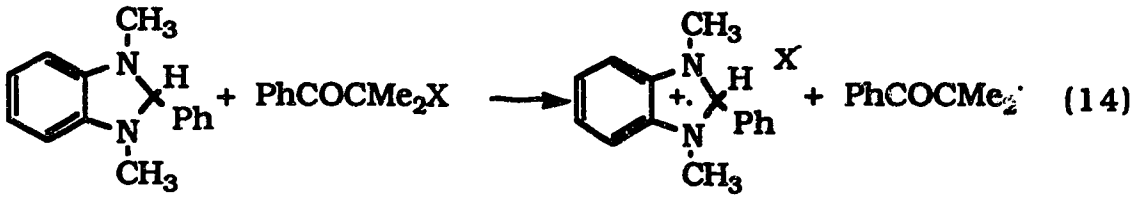
(20)

$$PhS^- + PhCOCMe_2X \longrightarrow PhCOCMe_2SPh + X^- \qquad (21)$$

ionic pathway involving S_N2 attack of PhS^- on $PhCOCMe_2X$ (eq 20-21). The small amount of **IIIc** formed in the absence of DNB arises from the slower S_N2 reaction. In the presence of DNB, the rapid free radical chain reaction was inhibited, and the slower ionic reaction becomes the dominant pathway.

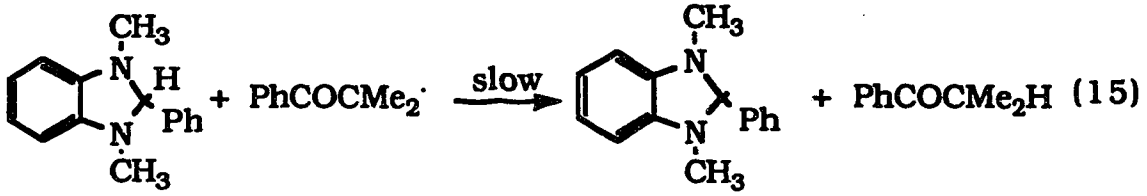
Scheme II-4 rationalizes the experimental results and seems to indicate that the thiophenol promoted reduction proceeds by a short chain process. The two main chain transfer steps involve hydrogen atom transfer from PhSH and DMBI (eq 15 and 16). Although the hydrogen abstraction from PhSH is well documented, the hydrogen abstraction of PhS· from C-H is limited by reversibility.[15,16] The major portion of the thiyl radicals produced results in dimerization (eq 19). A similar mechanistic scheme involving hydrogen abstraction from RSH by an aminyl radical, followed by hydrogen abstraction from the α-carbon of an amine by the RS· radical, was proposed to rationalize the catalytic effect of thiols in the photoreduction of benzophenone by amines.[17] In order to unambiguously show that the hydrogen abstraction of PhS· from DMBI (eq 17, Scheme II-4) does occur the reduction of diphenyl disulfide by DMBI was investigated.

initiation



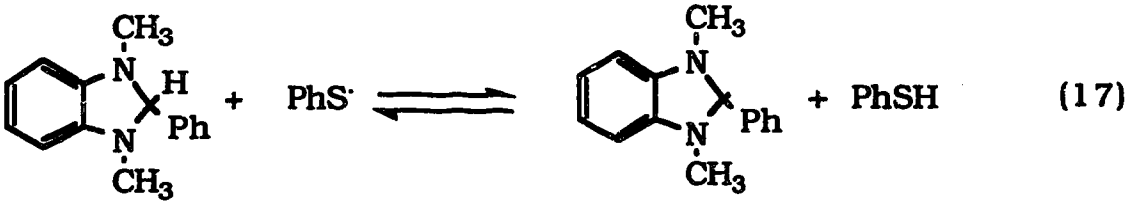
(14)

propagation

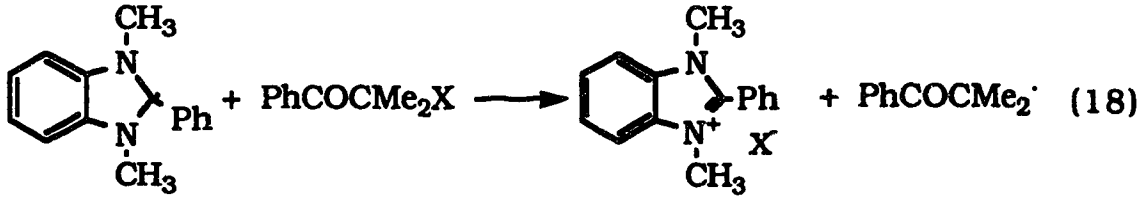


(15)

(16)



(17)



(18)

termination 2 PhS· ⟶ PhSSPh (19)

Scheme II-4. The Thiophenol Promoted Free Radical Chain Reduction of α-Haloisobutyrophenones by DMBI

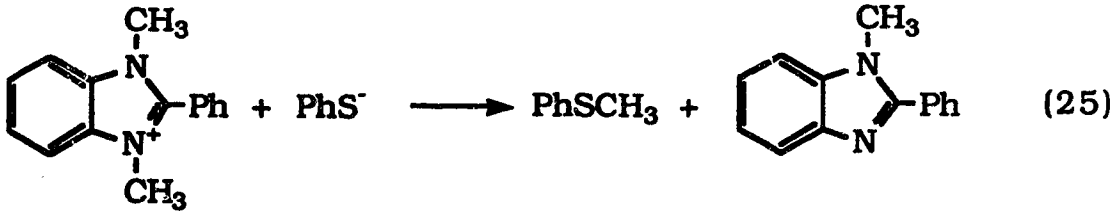
6. The Reduction of PhSSPh by DMBI

The reduction of diphenyl disulfide (PhSSPh) by DMBI was carried out in THF and C_6H_6 at 61 °C. The results are shown in Table II-8. The reduction can be initiated by AIBN to give thiophenol as the major product. Small amounts of methyl phenyl sulfide and 1-methyl-2-phenylbenzimidazole (< 6%) were also observed. These products are presumably formed by an S_N2 reaction of PhS^- with the 1,3-dimethyl-2-phenylbenzimidazolium cation (eq 25).[18]

Table II-8. The Reduction of PhSSPh by DMBI at 61 °C

Reaction	Solvent	Conditions [a]	PhSH	PhSSPh	$PhSCH_3$ [b]
59	THF	-	0.9 ± 0.9	73.4 ± 10	2.4 ± 0.7
60		7% AIBN	69.0 ± 0.4	20.7 ±3.0	6.4 ± 0.4
61	C_6H_6	-	-	94.0 ± 9.0	-
62		10% AIBN	72.2 ± 0.2	24.7 ± 5.0	1.2 ± 0.2

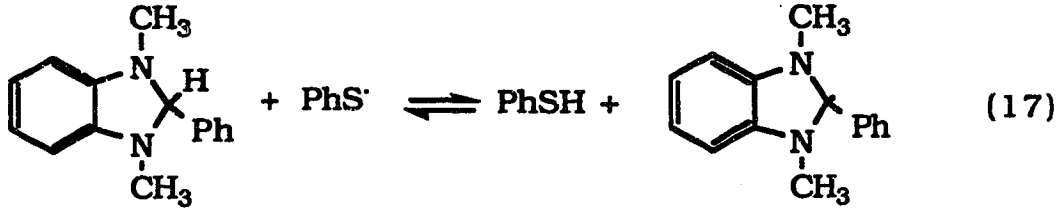
[a] [PhSSPh] = [DMBI] = 0.05 M; 10 h. [b] Small amounts (< 6%) of 1-methyl-2-phenylbenzimidazole were also observed.

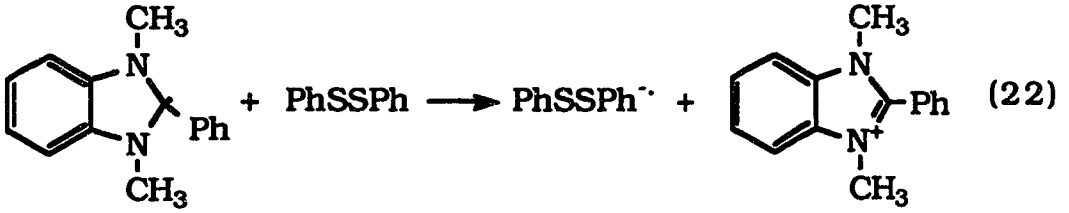


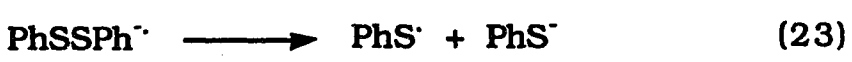
(25)

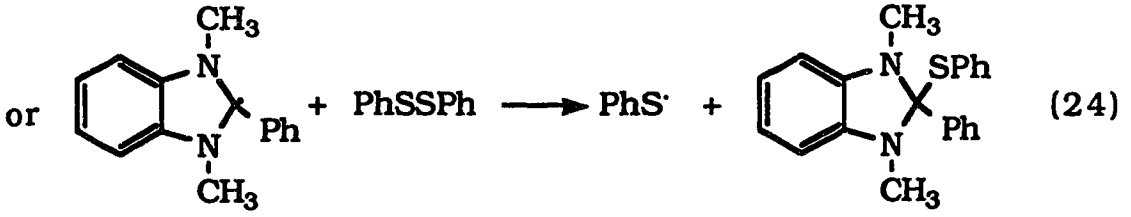
The initiation studies clearly establish that diphenyl disulfide is reduced by DMBI via a free radical chain sequence, and Scheme II-5 is proposed to account for this reduction. A similar radical chain sequence was proposed for the reduction of ArSSAr by *N*-benzyl-1,4-dihydronicotinamide (BNAH).[19]

propagation









termination

Scheme II-5. The Free Radical Chain Reduction of PhSSPh by DMBI

The chain propagation steps involve hydrogen abstraction of PhS· from DMBI and the regeneration of PhS· from PhSSPh and the DMBI radical. The first reaction (eq 17, Scheme II-5) is reversible. Thus the conversion of PhSSPh to PhSH was incomplete when only one equivalent of DMBI was employed. The regeneration of PhS· proceeds via either an electron transfer (eq 22-23) or an S_H2 attack at sulfur (eq 24).[20]

7. The Reaction of α-Haloisobutyrophenones with Thiophenol in the Presence of Triethylamine

Since α-(phenylthio)isobutyrophenone (**IIIc**) was formed by the DMBI (a base) assisted S_N2 attack of thiophenol on **IIIa-b** (eq 20-21), the reaction of **IIIa-b** with PhSH in the presence of another nitrogen base, triethylamine, was studied. The results of these studies are shown in Table II-9.

The reaction of α-bromoisobutyrophenone (**IIIa**) with PhSH/NEt_3 in THF and CH_3CN gave both the reduction and substitution products (reaction 63-69, Table II-9). The product ratio depends upon the solvent used; a higher yield of the reduction product was observed in THF than in CH_3CN. Moreover, the reaction proceeds much more readily in CH_3CN than in THF. Control experiments show that the reduction product does not arise from the substitution product (**IIIc**) since **IIIc** is unreactive under the conditions of the reaction. Similarly, **IIIa** is unreactive towards TEA in the absence of PhSH (RT, CH_3CN, 10 h). In both solvents, the reactions carried out in the presence of

Table II-9. The Reaction of $PhCOCMe_2X$ (IIIa-b) with PhSH/NEt_3

Reaction	X	Solvent	Conditions [a]	$PhCOCHMe_2$	$PhCOCMe_2SPh$	$PhCOCMe_2X$
63	Br	THF	RT, 1 h	55.2	18.5	22.1
64			RT, 1 h, 5% *p*-DNB	53.8	20.8	26.3
65			RT, 20 min	39.1	11.7	41.0
66			RT, 20 min, 100% *p*-DNB	36.3	12.3	51.5
67		AN	RT, air [b], 1 min	2.4	99	-
68			RT, 2.5 min	3.5	98	-
69			RT, 67 % *p*-DNB, 2.5 min	2	97	-
70	Cl	THF	RT, 18 h	-	6.5	98.8
71			61 °C, 17 h	-	15.3	87.4
72			61 °C, 86 h	-	54.3	44.6
73		AN	RT, 12 min	-	26.9	68
74			RT, 12 min, air [b]	-	26	75.7
75			RT, 12 min, 6% *m*-DNB	-	31.3	69.6
76			RT, 50 min	-	86.0	5.7
77	Br	THF	61 °C, DMA, [c] 64 h	8.3	2.8	79.7

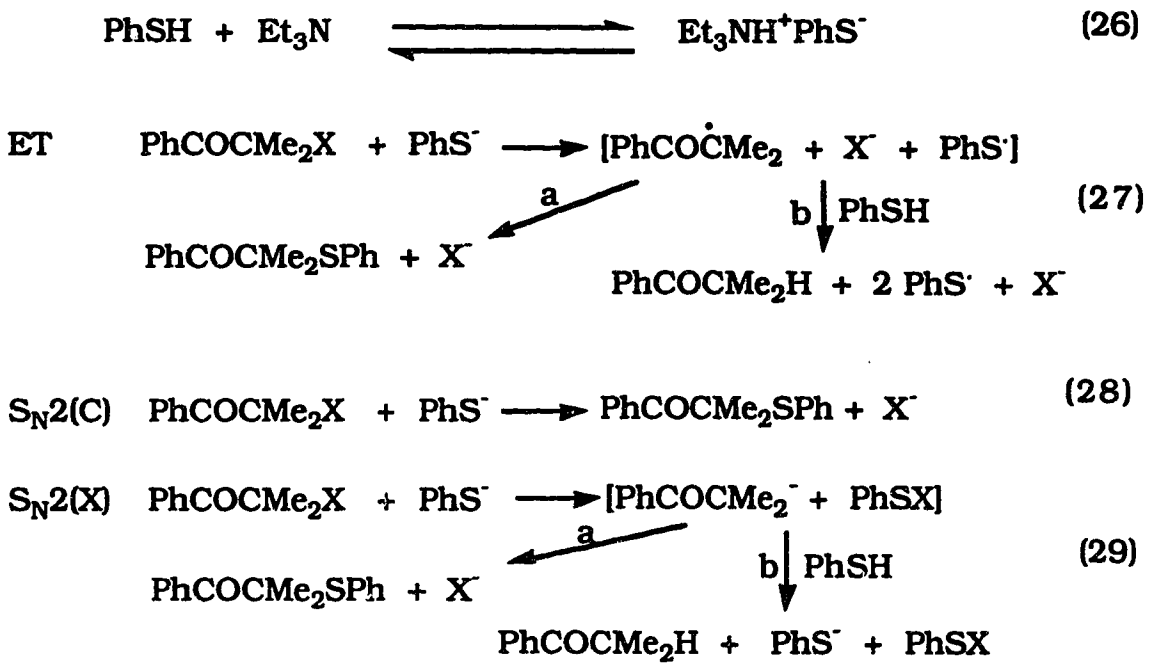
[a] All reactions were carried out in degassed solvents, unless where specified, with **[IIIa-b]** : [PhSH] : [TEA] = 1 : 2 : 2. **[IIIa-b]** = 0.05 M. [b] In undegassed solvents and mixed under air.
[c] *N,N*-Dimethylaniline (DMA) was used instead of TEA.

either dinitrobenzene (DNB) or molecular oxygen are not inhibited, nor is the product distribution affected (reactions 64, 66, 67, and 69, Table II-9).

The reaction of α-chloroisobutyrophenone (**IIIb**) proceeds more slowly than that of **IIIa** (reactions 70-76, Table II-9). The reaction of **IIIb** is also not affected by DNB or oxygen (reactions 73-75, Table II-9). In contrast to the reactions of **IIIa**, the reduction product ($PhCOCHMe_2$) was not observed in the reactions of **IIIb** in both THF and CH_3CN. The reaction of a secondary bromide, α-bromopropiophenone, also gave only the substitution product even in THF. The reduction product is therefore formed only in the reaction of the tertiary bromide **IIIa**.

When a weaker base, *N*,*N*-dimethylaniline (DMA), was used in the reaction of **IIIa** with PhSH, the reaction proceeded more slowly (compare reactions 77 and 63, Table II-9). This result suggests that PhS^- instead of PhSH is the reactive intermediate.

Three competing pathways are conceivable for the reaction of α-haloisobutyrophenones with PhSH in the presence of TEA: electron transfer (ET), eq 27; nucleophilic substitution at carbon ($S_N2(C)$), eq 28; and nucleophilic substitution on halogen ($S_N2(X)$), eq 29 (see Scheme II-6).



Scheme II-6. The Possible Mechanisms for the Reaction of α-Haloisobutyrophenones with PhSH/Et_3N

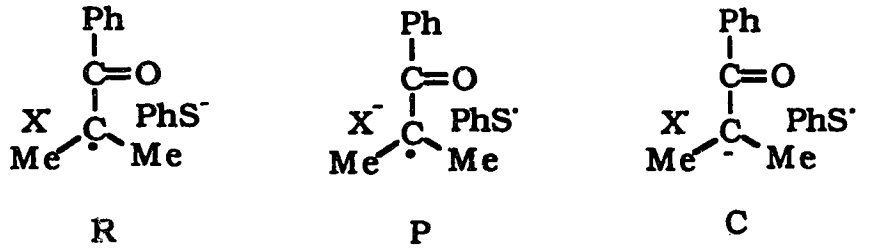
In the ET sequence, the ET between α-haloisobutyrophenones and PhS^- gives the radical pair ($PhCOC(CH_3)_2\cdot$ + PhS·) which either couples in the cage to produce the sulfide (**IIIc**) (eq 27a) or escapes the cage to ultimately give the ketone ($PhCOCHMe_2$) (eq 27b). The $S_{RN}1$ sequence[21] can be rejected since it is expected that the enolyl radical, $PhCOC(CH_3)_2\cdot$, would be rapidly trapped by PhSH before it has a chance to react with PhS^-. A nonchain ET sequence (eq 27) would not be affected by radical scavengers and by strong electron acceptors.

Similar ET nonchain mechanisms were first suggested by Russell[22] for the reaction of α-substituted nitroalkanes and have been discussed in detail by Bowman.[23]

Nucleophilic substitution on halogen atoms ($S_N2(X)$), X-philic reactions,[24] have been proposed as a mechanistic step in the reaction of a large number of halogen-substrates with nucleophiles. The $S_N2(X)$ sequence of reactions of α-haloisobutyrophenones with PhS^- produces an intermediate enolate anion ($PhCOCMe_2^-$) and a sulphenyl halide (PhSX) (eq 29, Scheme II-6). The enolate can either react with PhSX to give the substitution product (**IIIc**) or abstract a proton from PhSH (or NEt_3H^+) to form the reduction product ($PhCOCHMe_2$). A similar $S_N2(X)$ sequence has been proposed for the reaction of thiolates with α-halosulfones,[25] α-halonitroalkanes,[26] and 2-halomethyl-5-nitrofurans.[27]

Direct S_N2 substitution on tertiary carbons in pure acyclic aliphatic systems is extremely rare because of a competing S_N1 reaction. Tertiary α-halocarbonyl compounds, however, are believed to undergo S_N2 reactions,[28] since the competing S_N1 reaction is retarded by the electronegative carbonyl. A valence-bonding configuration mixing model,[29a] which has been used to explain the enhanced S_N2 reactivity of α-haloketones compared to alkyl halides,[29b] can provide a rationalization for the relative insensitivity of the S_N2 reaction of α-haloketones to steric effects. For the reaction of PhS^- with α-haloisobutyrophenones, three configurations (R, P, and C) are used to build the S_N2 reaction profile. The enolate configuration (C), which is impossible for pure alkyl halides, makes an important contribution to

the transition state, and decreases the steric effect associated with the S_N2 reaction.



According to Scheme II-6, the reduction product is produced by an ET (eq 27b) or $S_N2(X)$ (eq 29b) pathway. The substitution product (**IIIc**) in principle may be derived from all three pathways. Cage coupling is required for the ET or $S_N2(X)$ pathway. The $S_N2(C)$ mechanism is attractive since the ET or $S_N2(X)$ mechanism requires that the cage coupling reaction be competitive with diffusion of radicals or ions from the cage.

The reactions of α-haloketones with thiolates have been reported in several cases. Oki[30] reported that the reduction of an α-haloketone to its corresponding ketone proceeds by an intermediate α-alkylthioketone. Israel[31] found that substitution products were obtained in the reaction of α-chloro or α-bromoketones with RS^-, whereas reduction products were observed in the reactions of the corresponding α-iodoketones. A scheme involving $S_N2(X)$ attack of PhSH on the α-iodoketones was suggested. A similar change in reduction versus substitution ratios with different halogens was also observed for the

reaction of benzylic halides with PhSH/TEA.[32] In studies of the $S_{RN}1$ reactions of α-haloketones with nucleophiles, Russell[21] suggested that the reduction products observed are derived from the $S_N2(X)$ sequence although no experimental evidence was provided. The substitution reaction of α-chloro-*p*-nitroisobutyrophenone with PhS^- can be inhibited by DNB. On the other hand, the reaction of α-chloroisobutyrophenone (**IIIb**) with PhS^- was neither photostimulated nor retarded by t-$Bu_2NO\cdot$. Competing $S_{RN}1$ and S_N2 reactions were suggested as the mechanism for the reaction of the *p*-nitroketone, whereas only an S_N2 pathway was proposed for the reaction of **IIIb**.[21]

Since the reduction product was not observed for the reaction of α-chloroisobutyrophenone **IIIb** with PhSH/TEA, the $S_N2(C)$ pathway dominates the reaction of **IIIb**. With a less hindered substrate, α-bromopropiophenone, the $S_N2(C)$ pathway is also favored. A similar halogen effect and steric effect on competitive $S_N2(C)$ and $S_N2(X)$ pathways has been observed in the reaction of α-halosulfones with PhS^-.[25]

The formation of the reduction product during the reaction of the tertiary α-bromoketone, **IIIa**, suggests that with a hindered ketone a competitive reaction, $S_N2(X)$ or ET, takes place. The $S_N2(X)$ and ET pathways are difficult to differentiate. The steric and electronic effects on the two reactions are almost indistinguishable.

In a more polar solvent, CH_3CN, the yield of the reduction product for the reaction of **IIIa** was dramatically decreased. This observation seems to indicate that $S_N2(C)$ is favored in CH_3CN. No reasonable

explanation can, however, be offered for this dramatic change of mechanism with solvent polarity.

In summary, α-chloroisobutyropheone and α-bromopropiophenone react with PhSH/TEA to give their corresponding sulfides by the $S_N2(C)$ mechanism, whereas the reaction of α-bromoisobutyrophenone in THF gives both reduction and substitution products by competitive $S_N2(C)$, and $S_N2(X)$ or ET pathways. Solvent polarity seems to play an important role in determining the reaction mechanism. Finally, the PhSH/TEA system may be useful for the synthesis of α-phenylthioketones from α-haloketones.

Conclusions

Contrary to the original proposal,[6] the reduction of α-haloacetophenone compounds by DMBI was shown to proceed via a free radical chain mechanism for the primary and secondary halides. Although the tertiary halides do not undergo chain reduction due to inefficient hydrogen abstraction as one of the chain propagation steps, the reduction can be promoted by the presence of two equivalents of thiophenol as the chain transfer agent. These results show that DMBI is a good electron transfer reagent and has synthetic potential for the reduction of suitable electron acceptors. In the following chapters DMBI will be repeatedly used as the ET reducing agent for other α-substituted acetophenones and ring halogenated acetophenones. These reductions are used as compulsory ET reactions to deduce the mechanism of the reaction of substrates with different reducing reagents.

Experimental

1. Materials

The preparation or purification of **acetophenone**, **α-bromoacetophenone (Ia)**, **α-chloroacetophenone (Ib)**, **α-fluoroacetophenone (Ic)**, **2-fluoro-1-phenylethanol**, ***p*-di-*tert*-butylbenzene**, **α,α,-azobisisobutyronitrile (AIBN)**, and **dinitrobenzenes (DNB)** has been described previously.[2-5] **Tetrahydrofuran (THF)** (Aldrich, HPLC grade) was freshly distilled from $LiAlH_4$, and **acetonitrile (AN)** (Aldrich, HPLC grade) was distilled from CaH_2 before use. Commercial **benzene** (Fischer Scientific) was shaken with concentrated sulfuric acid (10% V/V) seven times, washed with water (three times), 10% sodium carbonate solution, water, and then dried over anhydrous calcium chloride. Benzene was fractionally distilled from CaH_2 and the middle fraction was collected and stored over molecular sieves (3A). Absolute **methanol** was obtained by treatment of commercial methanol (Terochem Laboratories Ltd.) with magnesium activated by iodine and stored over molecular sieves (3A).[33] **Triethylamine** (TEA) was distilled from and stored over CaH_2.

1,3-Dimethyl-2-phenylbenzimidazoline (DMBI) was prepared according to the literature procedure.[34] An ethanol solution of 2-phenylbenzimidazole (Aldrich) was methylated with methyl iodide in the presence of sodium ethoxide in an autoclave at 100 °C. The resulting 1,3-dimethyl-2-phenylbenzimidazolinium iodide was reduced by sodium borohydride in ethanol at room temperature. The pure

product was obtained by recrystallization from ethanol, mp 93-94 °C (lit.[35] 93-94 °C); ^{1}H NMR δ 2.58 (s, 6 H), 4.92 (s, 1 H), 6.4-6.5 (m, 2 H), 6.7-6.8 (s, 2 H), 7.4-7.5 (m, 3 H), 7.6-7.7 (m, 2 H). Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.28; H, 7.14; N, 12.49. Found: C, 80.32; H, 7.14; N, 12.62.

Di-*tert*-butylperoxyoxalate (DBPO) was prepared by the literature method.[7] Every precaution should be taken to avoid possible explosions when handling DBPO. During one preparation an explosion occured when attempting to collect the product in the filter flask after recrystallization at -78 °C. This might be caused by prolonged filtration so that the temperature of the solid rose to the room temperture and the solid was extremely dry.

(+)-3-Bromocamphor (or α-bromocamphor, IV) (General Intermediates of Canada) was recrystallized from ethanol and dried under vacuum over P_2O_5, mp 75-77 °C (lit.[36] 75-78 °C). **(±)-Camphor** (Eastman) was purified by sublimation, mp 174-175 °C (lit.[37] 175-177 °C).

Ethyl α-bromopropionate (V) (Fluka) was redistilled, bp 155-157 °C (lit.[37] 156-160 °C). **Ethyl propionate** (Aldrich, 97%) was used as received.

α-Bromopropiophenone (IIa) was prepared from propiophenone and copper bromide,[38] bp 140-143 °C (20 mmHg) [lit.[37] 245-250 °C]; ^{1}H NMR (80 MHz) δ 1.95 (d, 3 H), 5.25 (q, 1 H), 7.5 (m, 3 H), 8.0 (m, 2 H). **α-Bromoisobutyrophenone (IIIa)** (Aldrich, 98%), **propiophenone** (Aldrich, 99%), and **isobutyrophenone** (Aldrich, 97%) were redistilled and their purity, checked by GC, was found to be > 99%.

α-Chloropropiophenone (IIb) was prepared according to the literature procedure,[39] bp 105-108 °C (6 mmHg) [lit.[39] 78 °C (1.5 mmHg)]; ^{1}H NMR (80 MHz) δ 1.25 (d, 3 H, J = 7.5 Hz), 5.2 (q, 1 H, J = 7.5 Hz), 7.5 (m, 3 H), 8.0 (m, 2 H). **α-Chloroisobutyrophenone (IIIb)** was prepared according to the literature procedure,[40] bp 100-102 °C (2.2 mmHg) [lit.[40] 69-70 °C (0.4 mmHg)]; ^{1}H NMR (80 MHz) δ 1.85 (s, 6 H), 7.5 (m, 3 H), 8.15 (m, 2 H).

α-Fluoropropiophenone (IIc) was prepared from α-bromopropiophenone and potassium fluoride,[41] bp 85-90 °C (4.5 mmHg) [lit.[41] 105-107 °C (15 mmHg)]; ^{1}H NMR δ 1.65 (dd, 3 H, J_{HH} = 7 Hz, J_{HF} = 24 Hz), 5.65-5.70 (dq, 1 H, J_{HF} = 48 Hz), 7.5 (m, 5 H). Anal. Calcd for C_9H_9OF: C, 71.04; H, 5.96. Found: C, 70.77; H, 5.99.

1-Phenyl-1-octanone was prepared from *n*-octanoyl chloride by the Friedel-Crafts reaction,[42] bp 145-150 °C (2 mmHg) [lit.[43] 164 °C (15 mmHg)]; ^{1}H NMR (80 MHz) δ 0.9 (skewed t, 3 H), 1.4 (m, 10 H), 3.0 (t, 2 H), 7.5 (m, 3 H), 8.0 (m, 2 H). **1-Phenyl-2-methyl-1-octanone** was prepared similarly from 2-methyloctanoyl chloride, bp 158-160 °C (3 mmHg) [lit.[44] 130-131 °C (2 mmHg)]; ^{1}H NMR (80 MHz) δ 0.8 (skewed t, 3 H), 1.2-1.35 (m, 13 H), 3.5 (m, 1 H), 7.5-7.9 (m, 5 H). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.31; H, 10.03.

1-Phenyl-2,2-dimethyl-1-octanone was prepared according to the literature procedure[45] and purified by preparative gas chromatograph (Aerograph 1520) on a glass column (10 ft x 1/4 in.) packed with 20% FFAP on Chromosorb PAW, 60/80 mesh. Its structure was confirmed by analysis of its GC-MS spectrum (75 ft DB-1 glass capillary column); *m/e*: 232 (M^+), 207, 148, 126, 127, 105, 85, 71, 57, and 43.

Diphenyl disulfide (Eastman) was recrystallized from ethanol. **Thiophenol, thioanisole,** and **1-methyl-2-phenylbenzimidazole** were obtained from Aldrich and used as supplied. ***N,N*-Dimethylaniline** (Fischer Scientific) was used as received.

α-(Phenylthio)isobutyrophenone (IIIc) was prepared according to the literature procedure,[21] bp 160-170 °C (3.5 mmHg) [lit.[21] 141 °C (0.45 mmHg)]; ^{1}H NMR δ 1.6 (s, 6 H), 7.25-7.6 (m, 8 H), 8.2-8.32 (m, 2 H). MS: *m/e* 256 (M^+), 238, 223, 151, 105, 91, 77, 51, 41, and 28.

2. Methods and Procedures

Physical constants and microanalyses. All melting points were uncorrected and were obtained with a Mel-Temp or a Fischer-Johns melting point apparatus. Microanalyses were performed at the Microanalytical laboratory, Department of Chemistry, University of Alberta.

Spectral measurement. ^{1}H NMR spectra were recorded at 200 MHz unless otherwise indicated. Proton chemical shifts (in ppm) were reported with residual $CHCl_3$ (7.25) in $CDCl_3$ used as the internal standard. Mass spectra were obtained using an A.E.I. MS-50 high resolution mass spectrometer coupled to a Data General Nova 2DS-50. Gas chromatograph-mass spectra (GC-MS) data were obtained using either a Varian Aerograph 1400 gas chromatograph coupled to an A.E.I. MS-12 medium resolution mass spectrometer with the same packed columns as employed in the GC analyses or a Varian Vista 6000 gas chromatograph fitted with a glass capillary columns, DB-5 or

OV-351 (30 m x 0.25 mm, J&W Scientific), and coupled to a VG-70E mass spectrometer with an 1125 Data System. The former GC-MS apparatus was used to analyze the reactions described in the Sections 1-4 of Chapter 2 whereas the latter GC-MS apparatus was used to analyze all the other reactions described in this thesis. Gas chromatograph-infrared spectra (GC-IR) data were obtained using an HP 5965A IRD interfaced to an HP 5890 gas chromatograph (Hewlett Packard) was used to acquire the GC-IR data. Two capillary columns were used: Ultra-2 (25 m x 0.32 mm x 0.52 μm) and FFAP (50 m x 0.32 mm x 0.52 μm) (both from Hewlett Packard).

Quantitative gas chromatograph (GC) analyses. GC analyses were carried out on a Hewlett Packard 5840A gas chromatograph with a flame ionization detector and an HP 5840A terminal integrator.

To quantitatively calculate the yields of reaction products by GC analyses, a standard solution of known concentrations of the authentic products and internal standard was made and analyzed by GC. The concentrations of the standard mixture are as close to the real reaction mixture as possible. The initial concentrations of the substrate (RX) and internal standard (S) are C_{RX} and C_S. A standard mixture of substrate (C^f_{RX}), internal standard (C^f_S), and product (P, C^f_P) was analyzed to give the relative area ratios: P, A^f_P/A^f_S; RX, A^f_{RX}/A^f_S. The reaction mixture was then analyzed to give the relative area ratios: P, A_P/A_S; RX, A_{RX}/A_S. The yields of the product P and the recovered RX were calculated using the following equations:

$$P\% = [(A_P/A_S)/(A^f_P/A^f_S)][(C^f_P/C^f_S)][C_S/C_{RX}] \times 100\%$$

$$RX\% = [(A_{RX}/A_S)/(A^f_{RX}/A^f_S)][(C^f_{RX}/C^f_S)][C_S/C_{RX}] \times 100\%$$

Several injections of the solutions were carried out to obtain the average relative area ratios. The products were identified by a comparison of their retention times, GC-IR spectra and GC-MS spectra with those of authentic samples.

Three columns (15-20 ft x 1/8 in.) were used in GC analyses: 10% FFAP on Chromosorb WAW DMCS (60/80 mesh), 5% OV-101 on Chromosorb WAW DMCS (100/200 mesh), and 5% SE-30 on Chromosorb WAW DMCS (60/80 mesh).

General procedure for the reactions. Reaction ampules were pyrex tubes with 10/30 joints attached. They were cleaned with chromic acid solution, water, concentrated ammonium hydroxide, and distilled water, and then oven dried (200 °C). The reaction mixture was made by mixing 1 ml of a stock solution of the substrate containing an internal standard and the additives and 1 ml of a stock solution of the reagent. The mixture was placed in the ampule, degassed by three freeze-thaw cycles (-198 °C) using a high vacuum system (2-3 μm) and sealed under vacuum. The degassed mixture was subsequently allowed to react under the desired conditions. After the reaction the reaction mixture was analyzed by GC to obtain the yields of the products and the recovered substrate. The products were identified by GC-IR and GC-MS for each new reaction. All the reactions were carried out in duplicate and the average yields of the products are given in the tables.

General procedure for the reduction of α-haloketones with DMBI. An aliquot of a solution of the ketone (0.10 M), *p*-di-*tert*-butylbenzene (0.025 M), DMBI (0.10 M), and the additive in the desired solvent was placed in a reaction tube, degassed, sealed, and thermostated at the specified temperature for the time indicated in the tables. The tube was opened and analyzed by GC using the OV-101 or FFAP column.

The reactions with added DBPO were run in H-shaped ampules. The two solutions were mixed after they were degassed, sealed, and thermostated at 23 °C.

General procedure for the competitive kinetic studies. The relative rate constants of the substrate RX to R'X ($k_{RX}/k_{R'X}$) towards DMBI were measured through the disappearance of the starting substrates or the appearance of the products RH and R'H according to the Ingold-Shaw equation.[46] Most of the relative rates were measured by monitoring the disappearance of the starting substrates using GC. The following procedure was used to calculate the relative rate constants.

1 ml of a stock solution of the two ketones (0.1 M in each of the ketone, RX and R'X), and internal standard (0.05 M) was analyzed by GC to obtain the initial values of the relative areas of each ketone to the internal standard ($(A_{RX}/A_S)^o$). The solution was then added to 0.1 mmol DMBI, and placed in a pyrex ampule, degassed, sealed, and thermostated at 61 °C in the dark for 24-120 h, depending on the reactivity of the ketones. For the reduction involving α-fluoro-acetophenone 3-5% of AIBN was used to initiate the reductions. The ampule was opened and analyzed by GC using the same analytical conditions that were used before the reaction. The relative rate

constant ($k_{RX}/k_{R'X}$) was calculated according to the following equation,

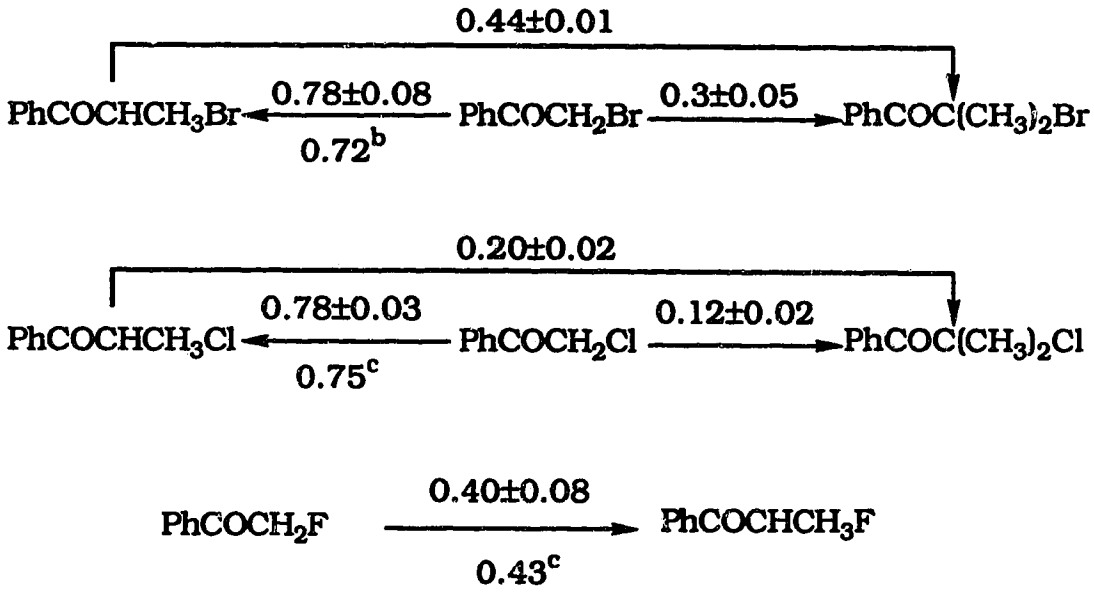
$$k_{RX}/k_{R'X} = \log[(A_{RX}/A_S)^o/(A_{RX}/A_S)^f]/\log[(A_{R'X}/A_S)^o/(A_{R'X}/A_S)^f]$$

where $(A_{RX}/A_S)^f$ was the area ratio of RX to the internal standard (S) after the reaction was completed. The results of the relative reactivities actually measured were schematically illustrated in Scheme II-7. The results shown in Table II-5 were calculated from this scheme.

The competitive rate constants of the reduction of several ketones were also measured by ^{1}H NMR (200 MHz). 1 ml solution of the haloketones (0.1 M) and *p*-di-*tert*-butylbenzene (0.03 M) in THF-d_8 and 1 ml solution of DMBI (0.1 M) in THF-d_8 were placed in the separate arms of an H-shaped pyrex ampule. The ampule was degassed, sealed, and thermostated at 61 ^{o}C. The solutions were mixed and allowed to react for 48 h. The ampule was opened, the reaction mixture was filtered, and the filtrate was analysed by ^{1}H NMR and GC, see Scheme II-7. In several cases the relative rates were determined from the appearance of the reaction products. In this case, a THF solution of the two substrates (0.1 M each) and internal standard (0.02 M) and a THF solution of DMBI (0.01 M) were allowed to react at 61 ^{o}C in the dark for 2-5 days. The following equation

$$k_{RX}/k_{R'X} = \{[RH]/[RX]^o\}/\{[R'H]/[R'X]^o\}$$

was used to calculate the relative rates, where $[RX]^o$ and [RH] were the concentrations of the initial RX and the final reaction product RH, respectively.



[a] The reactions were carried out at 61°C in THF. Arrows indicate direct competitions; numbers are relative reactivities from molecule at the head of the arrow to that at the tail. Values reported are averages of two or more experiments. Unless otherwise stated the rates were determined from the disappearance of the starting substrates. [b] Analyzed by ^1H NMR spectroscopy. [c] Measured from the appearance of the products.

Scheme II-7. Summary of the Competitive Reductions of the α-Haloketones (I-III)[a]

General procedure for kinetic studies. 2 ml solution of the α-haloketones (0.10 M) and the internal standard (0.05 M), and 1 ml solution of DMBI (0.10 M) in THF were each placed in the separate arms of the H-shaped pyrex ampule. The ampule was degassed, sealed, and thermostated at 61 °C. The solutions in the two arms of the H-shaped pyrex ampule were mixed and allowed to react for the time specified. The ampules were then cooled with liquid nitrogen, opened, thawed, and analyzed by GC using the OV-101 column. Three series of reactions (RX + DMBI, R'X + DMBI, RX + R'X + DMBI) were run in one batch. The results are presented by Figs. II-1 to Fig. II-3.

General procedure for trapping the radical intermediates. Aliquot solutions of the haloketone (0.01 M), internal standard (0.005 M) and DMBI (0.01 M) in 1-hexene were prepared. The general procedure that was used for the reductions in other solvents was followed. After the reaction the solution was analyzed by GC on the OV-101 column. The products were identified by a comparison of their retention times, GC-IR spectra and GC-MS spectra with those of authentic samples. In the case of **IIIb**, the trapping product, 1-phenyl-2,2-dimethyl-1-octanone, was not detected by GC-MS and GC-IR. Its absence was confirmed by the comparison of the GC retention time of an authentic sample with the retention times of the products formed in the reaction.

General procedure for the reaction of IIIa-b with PhSH in the presence of DMBI or TEA. An aliquot of a THF solution of the ketone (0.05 M), thiophenol (0.1 M), the internal standard (0.02 M), DMBI or TEA (0.1 M), and the additive was placed in a reaction ampule,

degassed, sealed, and thermostated at the desired temperature for the specified time (see Tables II-7 and II-9). The ampule was opened and analyzed by GC using the SE-30 column.

General procedure for the reduction of PhSSPh by DMBI. An aliquot solution of PhSSPh (0.05 M), *p*-di-*tert*-butylbenzene (0.02 M), DMBI (0.05 M), and the additive in THF was placed in a reaction ampule. The general reaction procedure was followed. The reaction products were analyzed on the SE-30 column.

Cyclic voltammetry. Electrochemistry was performed on a Princeton Applied Research EG and G Par Model 175 Universal Programmer wave form generator interfaced to an Amel Model 551 potentiostat that provided feedback compensation for ohmic drop between the working and the reference electrodes. Cyclic voltammograms were recorded using a Princeton Applied Research Model RE 0076 X-Y recorder for scan rates up to 1 V/s, and a Tektronix 2430 digital oscilloscope equipped with a Hewlett-Packard Thinkjet printer for scan rates up to 1000 V/s. The electrochemical measurements were carried out at room temperature in AN containing the substrate (0.005 M) and the electrolyte, tetrabutylammonium perchlorate (0.1 M). The reference cell contained silver perchlorate (0.001 M) and the electrolyte (0.1 M) in AN. Its potential relative to SCE was measured for each run (+0.25 ± 0.02 V). A glassy carbon electrode was used as the working electrode. The electrode was cleaned between each scan with a fine polishing powder and washed with AN.

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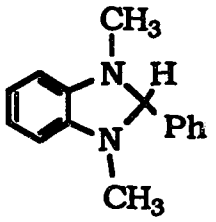
CHAPTER 3

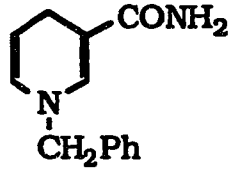
The Reductive Debromination of α-Bromocamphor by Tertiary Amines and Ammonium Formate via an Electron Transfer Hydrogen Abstraction Chain Mechanism

Introduction

Recently it was reported that the reduction of α-haloketones by 1,3-dimethyl-2-phenylbenzimidazoline (DMBI)[1] and *N*-benzyl-1,4-dihydronicotinamide (BNAH)[2] proceeds via an electron transfer hydrogen abstraction chain sequence (Scheme III-1), where one of the chain propagating species is the DMBI· or the BNA· radical.



DMBI



BNAH

initiation $RCOCR^1R^2X + ZH \longrightarrow RCOCR^1R^2X^{-\cdot} + ZH^{+\cdot}$ (1)

or
- Initiator $\longrightarrow In^{\cdot}$ (2)
- $In^{\cdot} + ZH \longrightarrow InH + Z^{\cdot}$ (3)

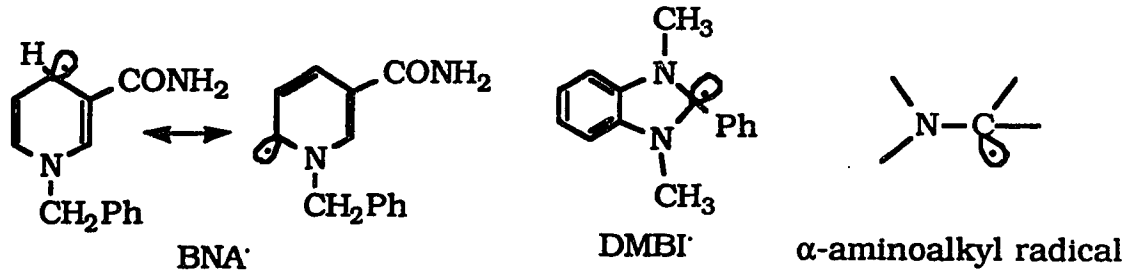
propagation
- $RCOCR^1R^{2\cdot} + ZH \longrightarrow RCOCR^1R^2H + Z^{\cdot}$ (4)
- $RCOCR^1R^2X + Z^{\cdot} \longrightarrow RCOCR^1R^2X^{-\cdot} + Z^{+}$ (5)
- $RCOCR^1R^2X^{-\cdot} \longrightarrow RCOCR^1R^{2\cdot} + X^{-}$ (6)

termination $2\,RCOCR^1R^{2\cdot} \longrightarrow (RCOCR^1R^2)_2$ (7)

ZH = DMBI, BNAH

Scheme III-1. The ET Chain Mechanism for the Reduction of α-Haloketones by a Hydride Donor ZH

Structurally DMBI· and BNA· radicals may be formally considered as α-aminoalkyl radicals. It is of interest to investigate the possibility that α-aminoalkyl radicals derived from simple tertiary amines might



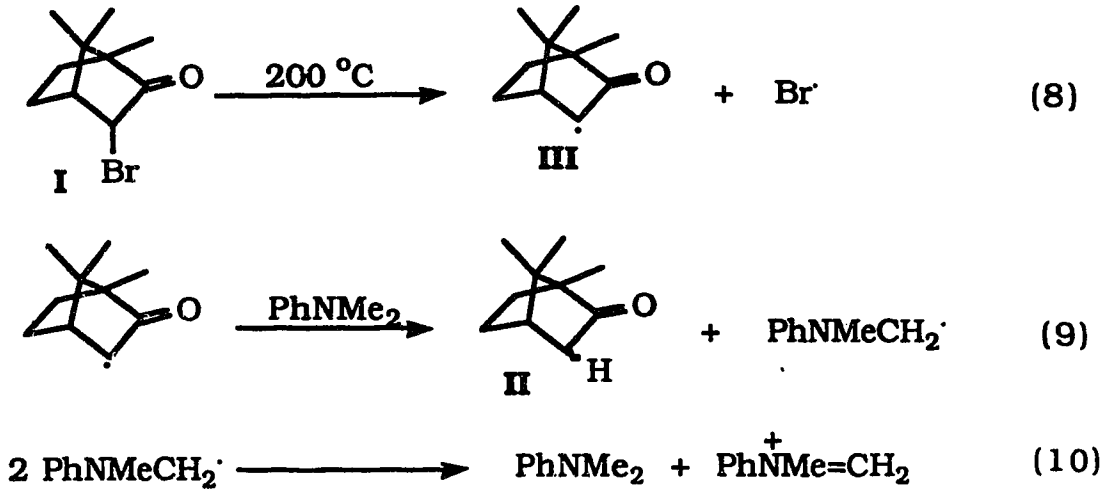
BNA· DMBI· α-aminoalkyl radical

undergo similar ET reactions with α-haloketones (Scheme III-1, ZH = amines). To investigate this possibility, we studied the reaction of α-bromocamphor with *N,N*-dimethylaniline and triethylamine.

Results and Discussion

1. The Reaction of α-Bromocamphor with Tertiary Amines

α-Bromocamphor (**I**) was selected as a model α-haloketone, since the S_N2 reactions of **I** are extremely slow.[3] Its debromination, to yield camphor (**II**), has been reported[3] using *N,N*-dimethylaniline (DMA) at 200 °C. Scheme III-2 was suggested for the debromination of α-bromocamphor by DMA. This mechanism assumes that the thermal cleavage of the carbon-bromine bond to give the camphor radical (**III**) occurs readily at 200 °C (eq 8). The bond dissociation energy (BDE)

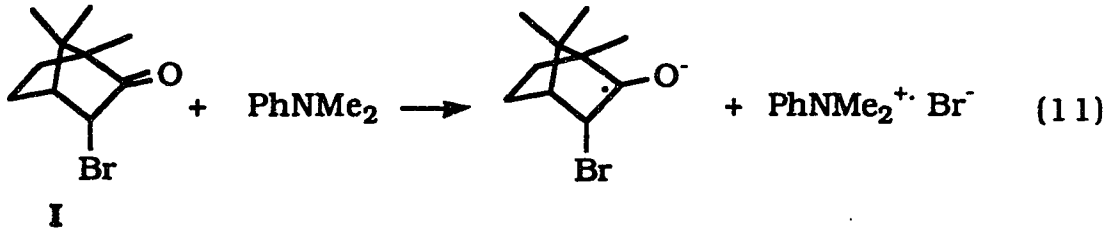


Scheme III-2. The ET Nonchain Mechanism for the Reduction of α-Bromocamphor by DMA

for the carbon-bromine bond in **I** is expected to be about 64 kcal/mol (the carbon-bromine bond dissociation energy for α-bromoacetone is 64 kcal/mol[4]). From a simple Arrhenius calculation it can be concluded that the thermal decomposition of **I** (eq 8) at 200 °C would not occur at any appreciable rate.[5] In fact, it was reported that the thermal decomposition of **I** itself at 200 °C yields only a small amount of camphor and no other detectable products.[3] Since the dehalogenation of α-haloketones by DMBI and BNAH proceeds via an ET mechanism (Scheme III-1), and since DMBI and BNAH may be considered as amines, a more likely mechanistic rationalization for the

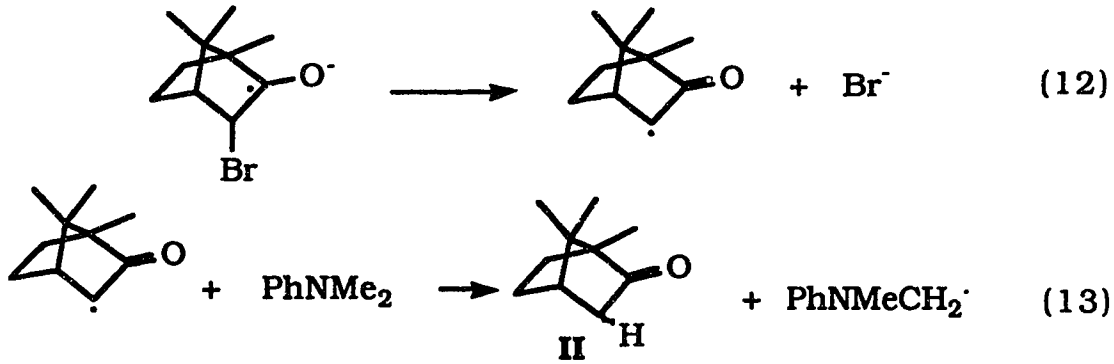
reported debromination of **I** is an ET free radical chain mechanism (Scheme III-3) similar to that shown in Scheme III-1.

initiation



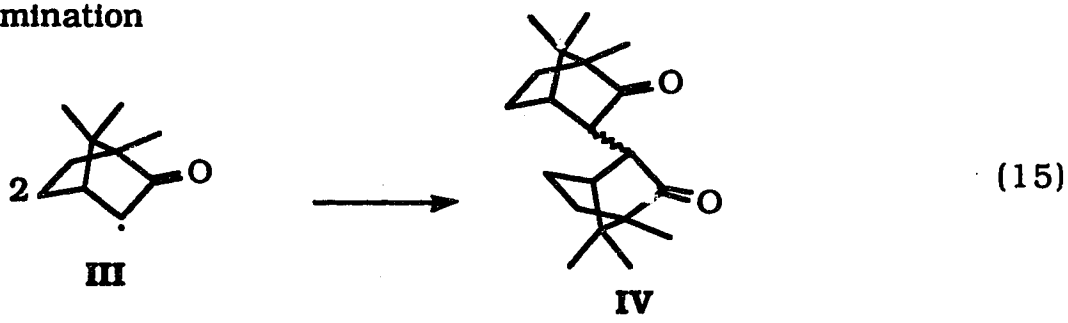
I

propagation



II

termination



III **IV**

Scheme III-3. The ET Chain Mechanism for the Reduction of α-Bromocamphor by DMA

Examination of Scheme III-3 and Scheme III-2 illustrates the major difference between the two mechanistic sequences: Scheme III-3 is a chain process and ET from the α-aminoalkyl radical of DMA to **I** is one of the chain propagation steps whereas Scheme III-2 is a nonchain process. In order to differentiate between these two mechanistic sequences (Scheme III-2 and III-3), the effect of an ET chain inhibitor, *p*-dinitrobenzene (DNB),[6] and a free radical chain initiator, di-*tert*-butylperoxide (BPO), on the reaction of **I** with DMA was studied. The results of these studies are listed in Table III-1.

The reduction of α-bromocamphor (**I**) to camphor (**II**) by DMA at 200 °C was inhibited by a small amount of DNB (Table III-1, reactions 1 and 2). Since the inhibition by DNB is consistent with a chain reaction, the ET hydrogen abstraction chain mechanism (Scheme III-3) is proposed for the reduction.

The initiation step for the radical chain reduction of **I** by DMA most likely is the ET from DMA to **I** (eq 11, Scheme III-3). The ability of amines to act as electron donors has been documented. The EPR spectra of quinone radical anions were observed in the reaction of amines with quinones at room temperature.[7] EPR spectra were also recorded in the reaction of methylglyoxal with amines.[8] The observation of the EPR spectra is attributed to the direct ET from the amines to the carbonyl compounds. The propagation steps involve the cleavage of the α-bromocamphor radical anion to give the camphor radical **III** (eq 12), the hydrogen atom abstraction of **III** from DMA (eq 13, Scheme III-3), and the ET from the α-aminoalkyl radical of DMA

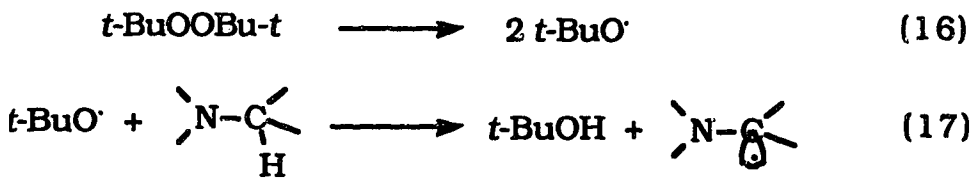
Table III-1. The Reduction of α-Bromocamphor (I) to Camphor (II) by *N,N*-Dimethylaniline (DMA) and Triethylamine (TEA)

Reaction	Amine	Conditions	Product Yield (%)	
			II	I
1	DMA	neat [a], 200 °C, 47 h	41.6 ± 0.6	63.4 ± 3.0
2		neat [a], 200 °C, 47 h, 4% DNB	1.3 ± 0.4	103.5 ± 3.0
3		AN, [b] 120 °C, 47 h	1.9 ± 0.2	98.0 ± 2.7
4		AN, [b] 120 °C, 47 h, 9% BPO	10.4 ± 0.9	92.4 ± 2.0
5	TEA	AN, [b] 120 °C, 47 h	2.2 ± 0.2	101.0 ± 2.2
6		AN, [b] 120 °C, 47 h, 11% BPO	101.5 ± 5.5	4.0 ± 0.7
7		neat, [a] 120 °C, 49 h	1.8 ± 0.1	93.4 ± 2.0
8		neat, [a] 120 °C, 49 h, 9% BPO	33.6 ± 4.3	61.4 ± 6.5

[a] [I] = 0.2 M. [b] [I] = 0.1 M, [amine] = 1.0 M

to I (eq 14, Scheme III-3). This mechanistic scheme receives further support from additional results shown in Table III-1.

When the reduction of I by DMA was carried out at 120 °C in acetonitrile (AN), only a low yield of camphor (1.9%) (Table III-1, reaction 3) was obtained. In the presence of BPO (5%) the yield increased to 10.4% (Table III-1, reaction 4). BPO undergoes homolysis at 120 °C in AN to produce the *tert*-butoxy radical (eq 16); its half-life ($t_{1/2}$) at 120 °C is estimated to be 12 h from the reported activation energy for the homolysis of BPO.[9] The *tert*-butoxy radical reacts quite efficiently with amines bearing α-hydrogens to produce α-aminoalkyl radicals (eq 17).[10] The α-aminoalkyl radicals could then participate in



the chain reduction of I (eq 14, Scheme III-3). It is thus expected that the thermal decomposition of BPO would initiate the radical chain reduction of I by DMA at 120 °C. The BPO initiated DMA reduction of I, however, yielded only 10.4% of camphor. The low yield of II at 120 °C in the BPO initiated reduction may be caused by the unfavorable ET step (eq 14, Scheme III-3) in the chain propagation sequence. Although the hydrogen abstraction step (eq 13) is also affected by temperature, the ET step is more likely the rate determining step. This suggestion is supported by the results obtained with

triethylamine (TEA) as the reducing agent (vide infra). Most likely the high temperature (> 200 °C) required for the reaction of I with DMA is necessary to ensure a reasonable rate of initiation and propagation.

The half-wave oxidation potentials ($E^{ox}_{1/2}$) for several α-aminoalkyl radicals have been reported.[11] Although these values were measured from the irreversible polarographic oxidation of α-aminoalkyl radicals and are not necessarily the same as the thermodynamically useful standard potentials (E^{o}), a qualitative comparison of the ET ability of α-aminoalkyl radicals for a series of amines can be made using these values. The α-aminoalkyl radical from TEA ($E^{ox}_{1/2}$ = -1.12 V, SCE, AN) is expected to be a better ET donor than the α-aminoalkyl radical from DMA ($E^{ox}_{1/2}$ = -0.85 V, SCE, AN).[11] In accordance with the ET chain mechanism, the BPO initiated reduction by TEA at 120 °C in AN gave camphor almost quantitatively (reactions 5 and 6, Table III-1), whereas the initiated reduction of I by DMA only yielded 10.4% of camphor (reaction 4, Table III-1). The ET step (eq 14, Scheme III-3) is therefore rate limiting in the overall chain sequence of the reduction of I by amines (DMA and TEA). In further support of this argument, the reduction of I by TEA proceeds more slowly in a less polar solvent, neat TEA (reactions 5, 6, 7, and 8, Table III-1) (dielectric constant, ε: TEA, 2.42; AN, 37.5).[12]

Electron transfer from an α-aminoalkyl radical to $PhCOCH_2HgCl$ was proposed as one of the chain propagation steps in the photostimulated free radical chain addition of $PhCOCH_2HgCl$ to enamines.[13] An ET from an α-aminoalkyl radical has also been suggested as one of the chain propagation steps in the addition of

perfluoroalkyl halides (R_fX) to enamines[14] and in the addition of alkylmercuryl halides to pyridine, pyridinium ions and *N,N*-dialkylanilines.[15]

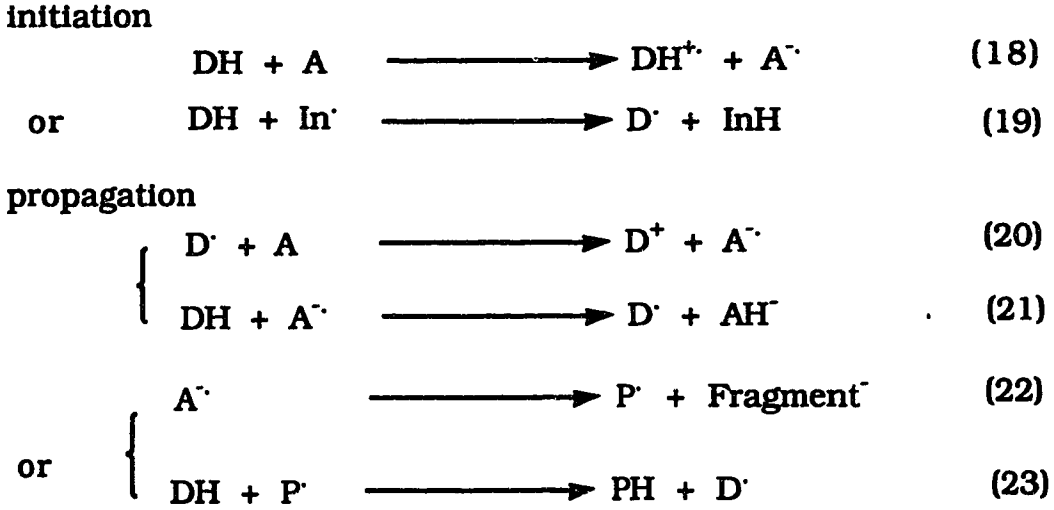
The α-aminoalkyl radical from triethanolamine was proposed as an electron donor in the photostimulated radical chain debromination of 2,3-dibromo-3-phenylpropionic acids ($E_{1/2}$ = -1.35 to -1.65 V, SCE, aq. AN).[16] More recently TEA was used to achieve the same debromination in the presence of another photosensitizer, $Ru(bpy)_3^{2+}$.[17] All these results indicate that α-aminoalkyl radicals derived from simple tertiary amines readily undergo ET reactions with suitable electron acceptors.

One possible termination step in the initiated free radical chain reduction of α-bromocamphor by amines is the dimerization of the camphor radical (eq 15, Scheme III-3). Three isomeric dimers of the camphor radical (**IV**, about 0.02% of the starting **I**, estimated from the GC-IR measurement) were observed in the reaction of **I** with TEA. When the initiated reaction with TEA was carried out in CD_3CN, the product, camphor, was found to have a very low deuterium content (2.8%). This result indicates that the majority of the hydrogen abstraction by the camphor radical takes place with TEA.

In summary the reductive debromination of α-bromocamphor by tertiary amines proceeds via the ET free radical chain mechanism shown in Scheme III-3. This mechanistic scheme may also be involved in the dehalogenation of other α-haloketones by DMA at high temperatures.[18]

2. A General Scheme for the Electron Transfer Activation

The reaction of amines with α-haloketones via an α-aminoalkyl radical intermediate is an example of ET activation where a more powerful (reducing or oxidizing) species is formed via an initiation process (ET or hydrogen abstraction). A general reaction sequence can be formulated for a net hydride transfer reaction (Scheme III-4).



Scheme III-4. A General ET Chain Mechanism for the Net Hydride Transfer Reaction between DH and A

This sequence should be energetically more favorable than an ET nonchain process (e.g. Scheme III-2) since the radical D· is usually a better ET donor than the parent compound DH.[11] This chain mechanism requires that (a) a suitable initiation process (eq 18-19) is available to produce one of the chain propagating species and (b) ET

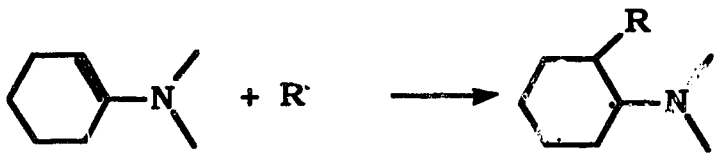
from D· and hydrogen atom abstraction from DH (eq 20-21) are not too slow to compete with direct hydride transfer. This scheme and its variants (for example, see eq 22-23, Scheme III-4) should be quite general, and yet have not received much attention in the discussions of net hydride transfer reactions.[19] The reduction of α-haloketones or α-nitrosulfones by triphenyltin hydride,[20] BNAH,[2,21] and DMBI [1,22] has been shown to proceed via this sequence of reactions.

Other examples of this type of ET activation include thermally initiated reductive dehalogenation of aryl halides by sodium methoxide,[23] and electrochemically[24] and photochemically[25] induced dehalogenation of aryl or alkyl halides by alcohols or alkoxides. The key steps in these reactions are the ET from the ketyl radical anion to the aryl or alkyl halides and the hydrogen abstraction from the alcohols or alkoxides by the aryl or alkyl radicals (eq 24-25).

$$RX + CH_2O^{-\cdot} \longrightarrow R^{\cdot} + X^{-} + CH_2O \qquad (24)$$

$$R^{\cdot} + CH_3O^{-} \longrightarrow RH + CH_2O^{-\cdot} \qquad (25)$$

The radical chain addition of $PhCOCH_2HgCl$[13] and R_fX[14] to the enamines discussed earlier is another type of ET activation. Here the alkyl radical adds to the enamine to produce an α-aminoalkyl radical which is a much better ET donor than the enamine itself and thus can transfer an electron to $PhCOCH_2HgCl$ or R_fX to propagate the chain reaction (eq 26-27).



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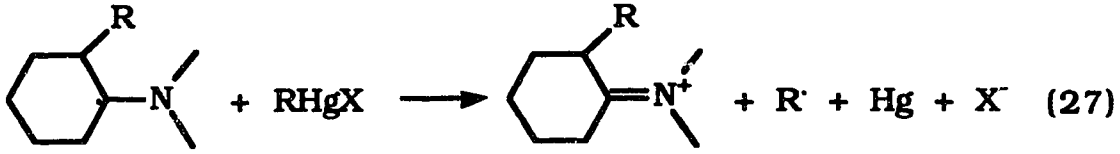

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3. Debromination of α-Bromocamphor with Ammonium Formate

In order to show the applicability of the general activation scheme discussed earlier in searching for new reactions, we carried out the reaction of α-bromocamphor with ammonium formate (Scheme III-4, DH = HCO_2^- , D· = CO_2^{-}·).

According to Scheme III-4, one of the chain propagation steps is the ET from D· (CO_2^{-}·) to the substrate (A). From the reduction potential of CO_2 (E^0 = -2.21 V, SCE, DMF),[26] it is clear that CO_2^{-}· is one of the strongest non-metallic reducing agents. It has been used to generate alkyl radicals from alkyl halides for EPR experiments,[27] and to reduce aryl diazonium salts via an ET chain mechanism.[28]

The reaction of ammonium formate with **I** was carried out at 115 °C in AN. The reagent was used in large excess due to its poor solubility in AN. At 115 °C it melts and the reaction may actually take place at the interphase. The results of the reaction are shown in Table III-2.

Table III-2. The Reduction of α-Bromocamphor (I) to Camphor (II) by Ammonium Formate

Reaction	Formate (eq)	Conditions [a]	Product Yield (%) II	I
9	48	48 h	12.7 ± 0.1	81.0 ± 1.0
10	48	48 h, 5% DNB	0.3 ± 0.1	100.1 ± 3.2
11	48	48 h, 10% BPO	85.2 ± 1.3 [b]	9.6 ± 0.7
12	15	48 h, 8% BPO	83.7 ± 1.0	11.3 ± 0.1
13	6	48 h, 8% BPO	41.1 ± 0.5	49.6 ± 0.6
14	2	48 h, 8% BPO	11.8 ± 0.1	79.6 ± 1.3

[a] All the reactions were run in AN at 115 °C with [I] = 0.2 M. [b] About 0.5% of camphor dimers were detected by GC-IR and GC-MS.

When 48 equivalents of ammonium formate were used, 12.7% of camphor was obtained. The reduction can be inhibited by DNB and initiated by BPO (see reactions 9, 10 and 11, Table III-2). The observation of the initiation by BPO and inhibition by DNB indicates that a free radical chain sequence is involved in the formation of camphor. The yield of camphor decreased dramatically when less than 6 equivalents of ammonium formate were used (reactions 13 and 14, Table III-2). If the initiated reaction was carried out in CD_3CN the product, camphor, showed a low deuterium incorporation (4.9%). These results indicate that most of the hydrogen in camphor arises from the hydrogen abstraction from formate by the camphor radical. As in the TEA reduction of I, the radical chain termination products

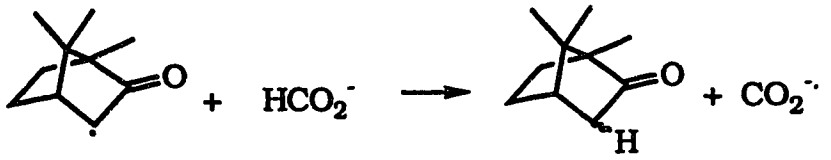
(the three dimers of camphor) were also observed in a very small amount. The total yield of the dimers was estimated to be 0.5%.

All these results suggest that a free radical chain reaction is involved in the reduction of α-bromocamphor by ammonium formate. The ET chain mechanism (Scheme III-5) is proposed for the reduction of I by ammonium formate. The chain termination step is the dimerization of the camphor radical (eq 15, Scheme III-5).

initiation

$$t\text{-BuO}^{\cdot} + HCO_2^- \longrightarrow CO_2^{-\cdot} + t\text{-BuOH} \qquad (28)$$

propagation



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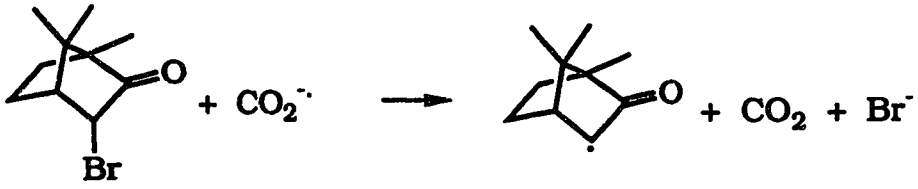
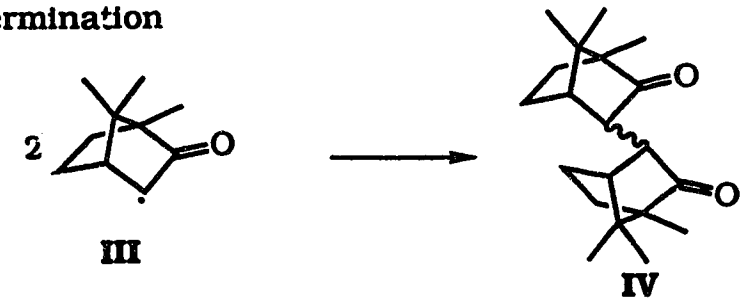


(30)

termination



(15)

III IV

Scheme III-5. The ET Chain Mechanism for the Reduction of α-Bromocamphor by Formate (HCO_2^-)

Conclusions

Contrary to the original proposal,[3] the reduction of α-bromocamphor to camphor by DMA at high temperatures (> 200 °C) proceeds via an ET chain sequence. The reduction can be effected with TEA in AN at much lower temperatures in the presence of BPO. The chain terimination step is the dimerization of the camphor radical. These results indicate that simple tertiary amines such as DMA and TEA could undergo an ET chain reaction with α-haloketones. BNAH[19,29] and DMBI[30] have been used as models for the enzymatic NADH reductions. The similar reactivity of TEA, BNAH, and DMBI towards α-haloketones demonstrates the possibility that simple amines such as TEA might also participate in the reactions effected by BNAH and DMBI.[31]

From the studies of the reduction of α-bromocamphor with amines, a general ET activation scheme is suggested for net hydride transfer reactions and applied to the reduction of α-bromocamphor by ammonium formate. α-Bromocamphor is reduced by ammonium formate to camphor through an ET chain sequence.

Experimental

1. Materials

The purification of **(+)-α-bromocamphor**, **camphor**, **acetophenone**, ***p*-dinitrobenzene**, ***p*-di-*tert*-butylbenzene** and **acetonitrile** is described in Chapter 2 of this thesis. **Di-*tert*-butylperoxide (BPO)** (Aldrich, 98%) and **ammonium formate** (BDH Chemicals Ltd., analytical grade, 97%) were used as supplied. **Triethylamine (TEA)** was distilled from calcium hydride before use. ***N*,*N*-dimethylaniline (DMA)**, Fischer Scientific, reagent grade) was distilled from a small amount of acetic anhydride.[32]

2. Methods and Procedures

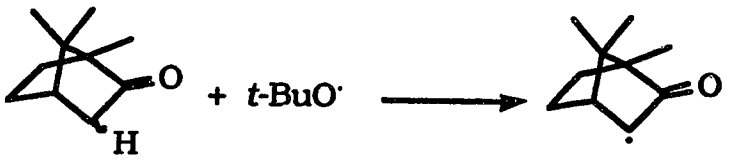
Physical constants, spectral measurements and GC analyses are described in Chapter 2.

General Procedure. An aliquot sample of a stock solution of α-bromocamphor (0.1 M or 0.2 M), *p*-di-*tert*-butylbenzene (0.05 M), and the additive in either neat amine or in AN containing the amine was placed in a reaction ampule. In the reactions with ammonium formate the reagent was added directly to the ampule. The ampule was degassed, sealed, thermostated at the desired temperature (200 °C or 120 °C, or 115 °C) for the time specified (see Tables III-1 and III-2). After the reaction, the ampule was cooled, opened and analyzed by GC using a stainless steel column (20 ft x 1/8 inch) packed with 5% SE-30 on Chromo WAW DMCS 80/100 mesh. Products were identified by

a comparison of their GC retention times, GC-IR (using a 50 m Ultra-2 capillary column) spectra and GC-MS (using a DB-5 capillary column) spectra with those of authentic samples. All reactions were carried out in duplicate.

The three dimers of camphor were detected by GC-MS in the reactions of **I** with both TEA and ammonium formate. Their MS spectra were nearly identical; *m/e*: 302 (M^+), 287, 274, 259, 246, 203, 193, 177, 151, 121, 108, 95, 83, 81, 79, 55, and 41. Their GC-IR spectra were similar to that of camphor. The total yield of the dimers was estimated using their IR intensities relative to camphor. In the reaction of **I** with TEA and ammonium formate the total yield of the dimers was 0.02% to 0.5% of the starting **I** (see the text).

Although no authentic samples of the dimers of camphor were available for comparison, the assignment of the dimers was supported by an indirect experiment. A degassed mixture of *dl*-camphor and BPO was heated at 150 ^{o}C for 4 h and analyzed by GC-IR under the same conditions used for the analysis of the reduction mixture of **I**. Three peaks having the same retention times and GC-IR spectra as observed in the reduction of **I** were detected and assigned to the camphor dimers. These dimers (**IV**) are produced from the dimerization of the camphor radical formed from the hydrogen abstraction of camphor by the *tert*-butoxy radical (eq 31 and eq 15).



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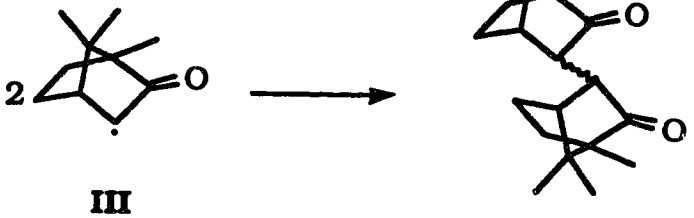

(15)

III IV

In the deuterium incorporation experiments, the reactions were carried out in CD_3CN and the same procedure outlined above was followed. The deuterium content of camphor (MW 152) was estimated from the GC-MS measurement of the reaction mixture. The intensities of the camphor-d_1 molecular ion (m/e, 153, M^+) and camphor-d_0 molecular ion (m/e, 152, M^+) were used to determine the deuterium content of camphor.

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5 From the reported BDE[4] and the activation energy[5a] of the homolysis of several alkyl bromides, the activation energy for the combination of alkyl radicals with the bromine atom (Br·) is estimated to be 4.5 ± 2 kcal/mol. The activation energy for the homolysis of **I** (eq 8, Scheme III-2) is expected to be 59.5 kcal/mol (E_a = 64 - 4.5 = 59.5). If the Arrhenius constant ($A = 2 \times 10^{13}$) reported for the homolysis of several alkyl bromides[5a] is used for the calculation of the rate constant for the homolysis of **I** at 200 °C (k_8), a value of 1.1×10^{-14} s^{-1} was obtained for k_8.

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CHAPTER 4

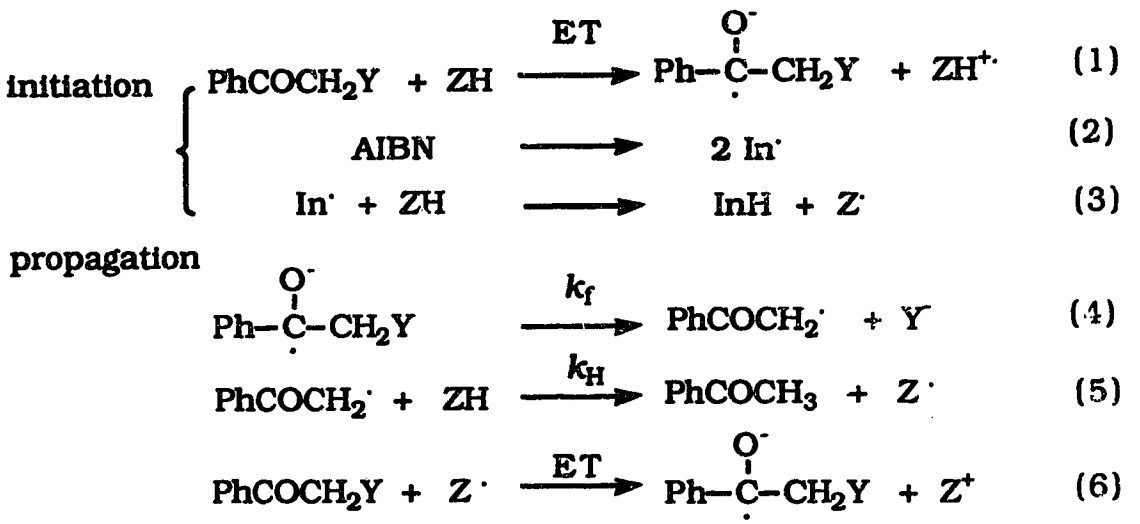
The Mechanisms of the Reduction of α-Substituted Acetophenones by DMBI and Ph_3SnH, and the Potential Use of These Ketones as an ET Probe

Introduction

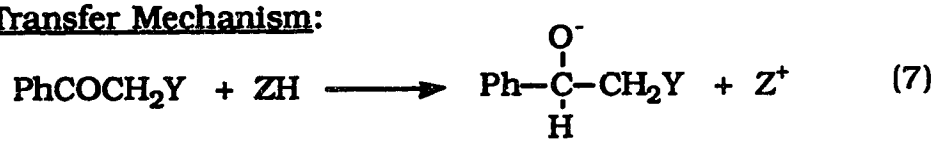
Reactions of nucleophiles with carbonyl compounds have been assumed to proceed by polar ionic mechanisms. In the past few decades, however, the importance of electron transfer (ET) processes in these reactions has been studied. EPR spectroscopy,[1] isotope effects,[2] *cis-trans* isomerization of enones,[3] and cyclizable probes[1a] have been used to differentiate between polar ionic and ET mechanisms (see Chapter 1). Liotta[4] and Miller[5] employed fragmentation probes to detect the ET reactions of ketones with organometallic compounds. The products formed from the cleavage of the radical anions of quinone monoketals[4] and quinol acetates[5] were thought to provide evidence for the ET mechanism. It is very difficult, however, to incorporate substituents into these probes to allow for the systematic study of the steric and electronic effects on ET reactions.

α-Haloacetophenones have been successfully used as a ketone fragmentation probe to differentiate between the hydride transfer and ET mechanisms (Scheme IV-1) in the reductions of ketones by organotin hydrides,[6] organosilanes,[7] 1,4-dihydropyridines,[8] and 1,3-dimethyl-2-phenylbenzimidazoline (DMBI).[9] The two mechanisms are distinguished on the basis of the products formed. Acetophenone is the product of an ET chain sequence (eq 1-6, Scheme IV-1) and the halohydrin is the product of a hydride transfer sequence (eq 7, Scheme IV-1). The halohydrin can also be the product of an ET nonchain sequence (eq 8, Scheme IV-1). The rate of the cleavage of α-haloacetophenone ketyls to give a halide ion (the leaving group) and

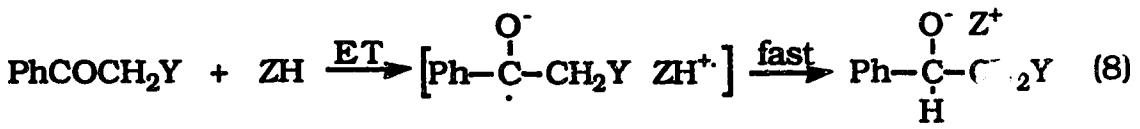
A. Electron Transfer Hydrogen Abstraction Chain Mechanism:



B. Hydride Transfer Mechanism:



C. Electron Transfer Nonchain Mechanism:

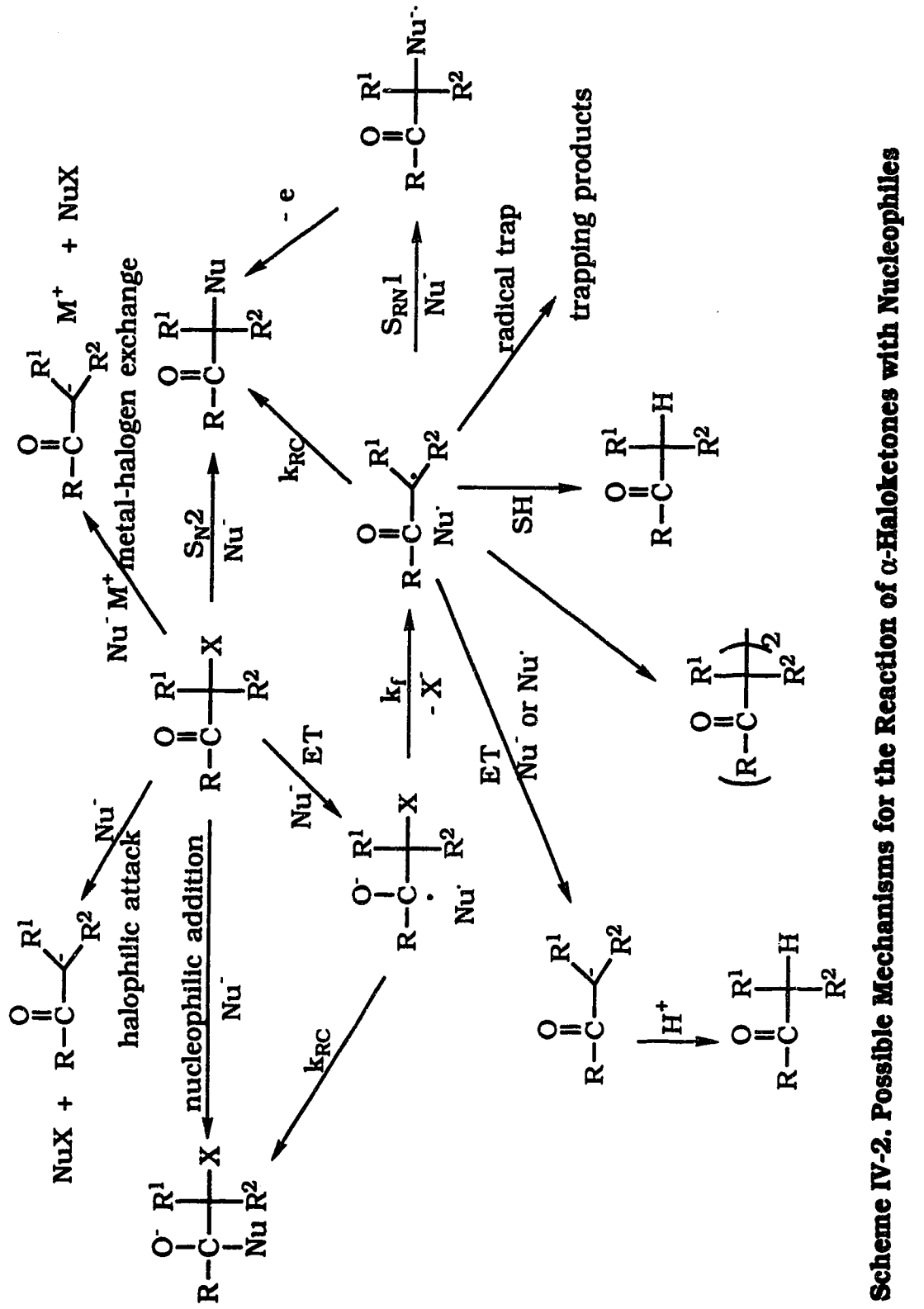


Y = Br, Cl, F, OCOR, SO_2Ar, OPh
ZH = R_3SnH, R_3SiH, BNAH, NADH, DMBI

Scheme IV-1. Possible Mechanisms for the Reduction of α-Substituted Acetophenones by Hydride Donors

an enolyl radical (eq 4, Scheme IV-1) is an important factor in the mechanistic differentiation. The fast cleavage of the ketyl yields acetophenone as the final product. If the cleavage of the ketyl is slow, the ketyl would abstract a hydrogen from ZH or $ZH^{+\cdot}$ to form the halohydrin. The ET mechanism is distinguishable from the direct hydride transfer mechanism if each process gives an unique product.

In the reaction of α-haloacetophenones with nucleophiles, the fast cleavage of the ketyls is also required to differentiate between an ET and an ionic mechanism. If the ketyl cleavage is slow the same nucleophilic addition product will be formed by a direct nucleophilic addition, or by an ET followed by radical couping (Scheme IV-2). The formation of the dehalogenated products indicates the involvement of an ET process. Several competing reactions of the α-haloketone probe with nucleophiles, however, may also give dehalogenated products. These competing reactions include metal-halogen exchange,[10] nucleophilic substitution,[10-11] and halophilic attack (i.e. nucleophilic attack on halogens).[12] To minimize the possible competing reactions, functional groups other than halogen can also be used as leaving groups in the ketyl cleavage reaction (eq 4, Scheme IV-1). These functional groups include $ArSO_2$, ArS, ArO, and ArCOO. The α-substituted acetophenone probe ($PhCOCH_2Y$, Y = Br, Cl, F, $ArSO_2$, ArS, ArO, and ArCOO) has an advantage over the ketone fragmentation probe of Liotta and Miller in that the α-substituted acetophenone probe allows substituents to be easily incorporated into the phenyl ring of the benzoyl moiety or into the phenyl ring of the leaving group (Y). The systematic study of substituent effects (steric and electronic) on ET reactions can be carried out using this probe. House has briefly studied the possibility of α-substituted isobutyrophenones (such as α-acetoxyisobutyrophenone) as an ET probe for the reaction of ketones with organocuprates.[13] This study suggests that the α-substituted acetophenone probe might be useful for the study of the ET reactions of ketones with a variety of nucleophiles.



Scheme IV-2. Possible Mechanisms for the Reaction of α-Haloketones with Nucleophiles

Before the new probe can be applied to the reactions with organometallic compounds and carbanions, it is essential to establish that the probe is a suitable electron acceptor and that the cleavage of the ketyl anion of the α-substituted acetophenone (eq 4, Scheme IV-1) is fast enough to compete with the hydrogen abstraction to form the alcohol (eq 8, Scheme IV-1). DMBI has been shown previously to be an excellent ET reducing agent for the reduction of α-haloacetophenones[9] and α-nitrosulfones.[14] In this chapter the reaction of other α-substituted acetophenones ($PhCOCH_2Y$, Y = $ArSO_2$, ArS, ArO, and ArCOO) with DMBI is used to study the electron accepting ability of these ketones. These ketones are then used as probes to study the mechanisms of the reduction of ketones by Ph_3SnH. In Chapter 5 of this thesis the measurements of the cleavage rate constants of several α-substituted acetophenone ketyl anions are reported.

Results and Discussion

The compounds studied in this chapter are $PhCOCH_2Y$ (**Ia-f**; **a**, Y = OCOPh; **b**, Y = $OCOCH_3$; **c**, Y = $OCOC_6H_2Me_3$-2',4',6'; **d**, Y = OPh; **e**, Y = *p*-$TolSO_2$; **f**, Y = PhS), $PhCOCHCH_3SO_2Tol$-*p* (**II**) and $PhCOCMe_2SO_2Tol$-*p* (**III**) and $PhCOCMe_2SPh$ (**IV**). Reductions using Ph_3SnH were carried out in benzene, whereas reductions using DMBI were carried out in benzene or in THF. The results of the reductions are shown in Table IV-1. All the reactions require AIBN initiation (in the absence of AIBN there is no appreciable reaction (< 5%)) suggesting that a free radical chain mechanism is involved in these

Table IV-1. The Reduction of α-Substituted Acetophenones by DMBI and Ph_3SnH

Reaction	Compound $PhCOCR^1R^2X$	Method [a]	Product (%) [b] $PhCOCHR^1R^2$ [c]	$PhCOCR^1R^2X$
1	**Ia**	A	90.0 ± 0.1	3.2 ± 1.0
2		B	95.8 ± 2.7	-
3	**Ib**	A	55.1 ± 1.0	45.3 ± 1.0
4		B	72.7 ± 0.5	15.4 ± 0.9
5	**Id**	A	11.9 ± 0.7	81.0 ± 3.0
6	**Ie**	C	94.8 ± 0.7	-
7		D	94.3 ± 4.1	-
8	**II**	C	94.4 ± 2.2	-
9		D	100.0 ± 1.0	-
10	**III**	C	16.0 ± 1.0	81.8 ± 3.0
11		D	92.4 ± 2.0	-
12	**If**	C	86.1 ± 0.7	12.3 ± 4.0
13		D	95.0 ± 4.0	-

[a] All reactions were carried out at 61 °C in the dark with [ketone] : [reducing agent] : [AIBN] = 1 : 1.2 : 0.05. [ketone] = 0.05 M. A, DMBI, benzene, 60 h; B, Ph_3SnH, benzene, 60 h; C, DMBI, THF, 48 h; D, Ph_3SnH, benzene, 48 h. [b] Average of at least two runs. [c] In the reductions by Ph_3SnH a small amount (< 5%) of $PhCHOHCR^1R^2$ was also observed by GC on the FFAP column.

reductions. Since the reduction of the structurally analogous α-halo-acetophenones by DMBI has been proposed to proceed by an ET chain sequence,[9] the free radical chain reduction of other α-substituted acetophenones by DMBI most likely proceeds by the same ET chain sequence (eq 1-6, Scheme IV-1). DMBI is therefore used as a compulsory ET reducing agent to establish the possible involvement of an ET process in the free radical chain reduction of the α-substituted acetophenones by Ph_3SnH.

1. The Reductions of the α-(Carbonyloxy)acetophenones (Ia-c)

The reduction of **Ia-b** by Ph_3SnH and DMBI gave only acetophenone (Table IV-1, reactions 1-4); no alcohols ($PhCHOHCH_2X$, X = OCOPh, and $OCOCH_3$) were obtained. Qualitatively the benzoate (**Ia**) is more reactive than the acetate (**Ib**). DMBI and Ph_3SnH show similar reactivities towards **Ia-b**.

The reduction of **Ia-b** by DMBI most likely proceeds by the ET chain sequence shown in Scheme IV-1 (eq 1-6). In the chemical[15a] and the electrochemical[15b] reduction of α-(carbonyloxy)ketones, the α-(carbonyloxyl)ketyl undergoes cleavage to give an enolyl radical. Since no alcohol is observed in the DMBI reduction of **Ia-b**, the cleavage of the ketyl of **Ia-b** must be fast and the ET process is favored over the hydride transfer process.

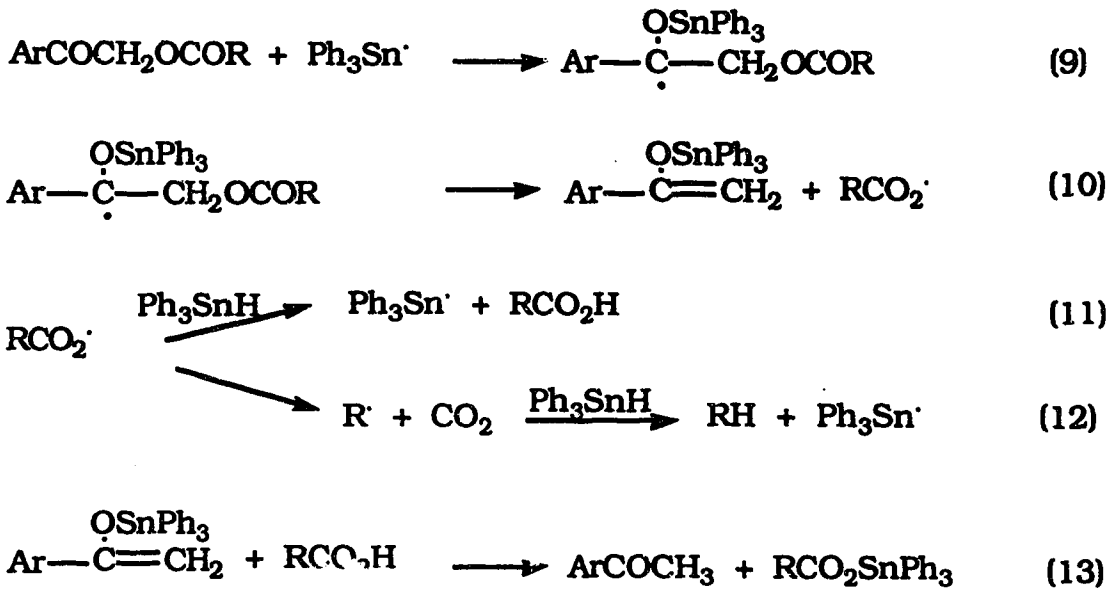
Phenacyl and *p*-bromophenacyl are useful protecting groups for carboxylic acids and phenols.[16] The protecting groups can be removed by the treatment of the substrates with zinc in acetic acid[16b] or with

PhS^-M^+ in DMF.[16c,d] Since phenacyl esters of both aromatic and aliphatic acids (**Ia-b**) can be easily reduced to their corresponding acids by DMBI, the reaction of phenacyl esters with DMBI provides a selective deprotection method for carboxylic acids under neutral and mild conditions.

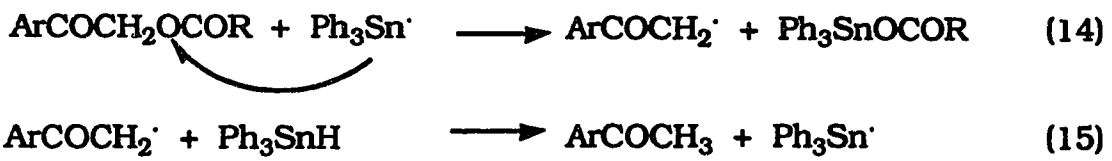
In the free radical chain reduction of **Ia-b** using Ph_3SnH, one of the chain propagating species must be the $Ph_3Sn\cdot$ radical. From the known chemistry of tin radicals,[17] several mechanistic pathways can be envisioned for the reduction by Ph_3SnH. Since the tin hydride reduction of a structurally similar compound, α-fluoroacetophenone, gives acetophenone and proceeds by an ET chain sequence (pathway A, Scheme IV-1, X = F, ZH = Ph_3SnH),[6] the reduction of **Ia-b** by Ph_3SnH might also proceed by the same chain sequence (pathway A, Scheme IV-1, ZH = Ph_3SnH, X = OCOPh, $OCOCH_3$). Other possible free radical chain sequences, shown in Scheme IV-3, include the $Ph_3Sn\cdot$ addition to the ketone carbonyl followed by β-elimination (pathway A), the $Ph_3Sn\cdot$ addition to the ester carbonyl (pathway C), and the $Ph_3Sn\cdot$ displacement at ethereal oxygen (S_H2, pathway B).

According to pathway A (Scheme IV-3) the intermediate radical is $RCO_2\cdot$ which could either abstract a hydrogen or decompose to give CO_2 and R· (eq 11-12, Scheme IV-3). The major difference between pathway A (Scheme IV-3) and the other proposed pathways (pathway A, Scheme IV-1; pathway B and C, Scheme IV-3) is that the enolyl radical ($PhCOCH_2\cdot$) is not an intermediate in pathway A (Scheme IV-3). In order to establish whether $PhCOCH_2\cdot$ is an intermediate in the Ph_3SnH reduction of **Ia-b**, a trapping experiment using 1-hexene was

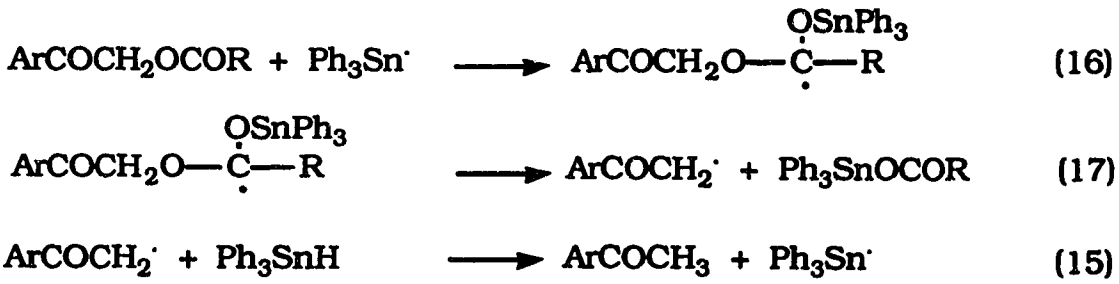
A. Addition Elimination Mechanism (on Ketone Carbonyl):



B. S_H2 Mechanism:



C. Addition Elimination Mechnism (on Ester Carbonyl):



Scheme IV-3. Possible Mechanisms for the Free Radical Chain Reduction of α-(Carbonyloxy)acetophenones

carried out. In order to obtain a homogeneous solution the reaction of **Ia** (0.01 M, 5% AIBN) with Ph_3SnH (0.01 M) was carried out in 1-hexene containing 11% of benzene at 61 °C. After 7 days, a 10.2% yield of acetophenone, a 26.3% yield of 1-phenyl-2-octanone, and a 60.3% yield of recovered **Ia** were obtained. Similarly, the reduction of α-fluoroacetophenone gave a 6% yield of acetophenone, a 9.1% yield of 1-phenyl-2-octanone and a 90% yield of α-fluoroacetophenone. Under the same conditions acetophenone did not give 1-phenyl-2-octanone. The control experiment shows that the trapping product, 1-phenyl-2-octanone, is formed from the reduction of **Ia**, but not from the product acetophenone.

The formation of the trapping product, 1-phenyl-2-octanone, could only be explained by the intermediacy of the $PhCOCH_2\cdot$ radical (see Chapter 2 of the thesis for similar trapping experiments in the reduction of α-haloacetophenones with DMBI). The addition of the enolyl radical to 1-hexene gives a new alkyl radical which abstracts a hydrogen from Ph_3SnH to carry the chain. The trapping experiment demonstrates that pathway A (Scheme IV-3) is not involved in the tin hydride reduction of **Ia**. Similarly, the trapping experiment also rules out the possibility of the addition elimination mechanism for the tin hydride reduction of $PhCOCH_2F$ and further substantiates the previously proposed ET mechanism.[6a]

The difference between the ET (pathway A, Scheme IV-1) and the S_H2 pathway (pathway B, Scheme IV-3) is more subtle. The reaction of tin hydrides with peroxides was reported to proceed by the S_H2 mechanism, although an ET step was proposed as an alternative

mechanism.[18] The S_H2 mechanism is expected to be sensitive to steric effects. Thus di-*tert*-butylperoxide reacts with tributyltin hydride about 500 times slower than diethylperoxide.[18] In order to assess steric effects on the reduction of α-(carbonyloxy)acetophenone the relative rate constants (k_{Ic}/k_{Ia}) of the reduction of a sterically hindered ester, **Ic** (α-(2',4',6'-trimethylbenzoyloxy)acetophenone), to the reduction of the parent compound, **Ia**, were measured at 61 °C for the reduction by Ph_3SnH and DMBI. The k_{Ic}/k_{Ia} values for Ph_3SnH (0.76 ± 0.13) and DMBI (0.95 ± 0.07) are almost the same and close to 1.0. These results indicate that a steric effect at the ester site is not important for the reduction by these two reagents. The tin radical addition to the ester carbonyl (pathway C, Scheme IV-3), therefore, seems unlikely.

Another indication that the reaction site is not at the ester site (i.e. pathways B, Scheme IV-3) comes from the absolute rate constants of the reaction of tributyltin hydride with acetophenone (~ 1.0×10^6 M^{-1} s^{-1}, 25 °C)[19] and benzyl benzoate (3.5×10^3 M^{-1} s^{-1}, 25 °C).[18] These results suggest that pathways B and C (Scheme IV-3) are unlikely for the tin hydride reduction of **Ia-c**. The ET chain sequence is then left as the best candidate for the reaction mechanism.

A deoxygenation method has been developed for the α-hydroxy-ketones of sugars via the reaction of the benzoate of the α-hydroxy-ketones (-CR(OCOPh)CO-) with tin hydrides.[20,21] The reaction was first reported to proceed via tin radical addition to the ester carbonyl oxygen of the benzoate and the subsequent carbon-oxygen bond cleavage to give the tin benzoate and the alkyl radical[20] (similar to

pathway C, Scheme IV-3). This mechanism seems unlikely since no reaction occurs in the absence of the keto group[21] and since a ketone or an aldehyde is generally more reactive than esters towards tin radicals.[22] It was later assumed that the keto group is being attacked[17] (similar to pathway A, Scheme IV-3). Our results from the studies of the reactions of **Ia-c** with triphenyltin hydride suggest that a similar ET chain mechanism might also be involved in this reductive deoxygenation. Detailed studies of this reaction, however, are required to draw a more definitive conclusion.

2. The Reductions of α-Phenoxyacetophenone (Id)

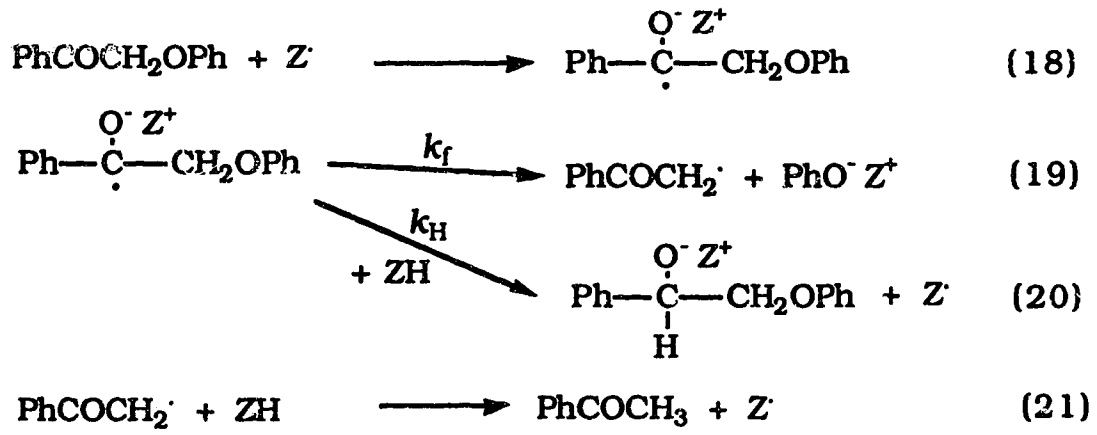
From a comparison of the product yields obtained under similar reaction conditions, the reduction of α-phenoxyacetophenone (**Id**) by DMBI and Ph_3SnH (see reaction 5, Table IV-1; reactions 14-17, Table IV-2) seems to be slower than the reduction of **Ia-b** (reactions 1-4, Table IV-1). The reduction by DMBI gave only acetophenone, whereas the reduction with tin hydride gave acetophenone and 2-phenoxy-1-phenyl-1-ethanol. The tin hydride reduction of **Id** was examined at several different tin hydride concentrations. The percentage of the alcohol increased as the concentration of the tin hydride was increased (see Table IV-2). Since the reduction did not take place in the absence of AIBN, it appears that both products are formed by a free radical chain mechanism.

Table IV-2. The Reduction of α-Phenoxyacetophenone (Id) by Ph_3SnH

Reaction	$[Ph_3SnH]$ M	Conditions [a]	Product (%) [b]			
			PhCOMe	PhCHOHMe	$PhCHOHCH_2OPh$	Id
14	0.05	66 h	7.2	-	26.5	66.4
15	0.10	66 h	5.6	6.[illegible]	33.3	38.5
16	0.15	66 h	2.9	8.[illegible]	78.7	-
17	0.15	69 h [c]	-	-	-	99.7

[a] All reactions were run at 61 °C in benzene in the dark with [Id] = 0.05 M. 5% AIBN was used except in reaction 17. [b] measured by ^1H NMR. [c] No AIBN was used in this case.

The ET chain mechanism (Scheme IV-4) is consistent with our experimental observations. The ketyl radical anion formed upon ET to **Id** (eq 18) either cleaves to give the enolyl radical (eq 19) or abstracts a hydrogen to give the alcohol (eq 20). In the reaction with DMBI the hydrogen abstraction (eq 20) is much slower than the ketyl fragmentaion (eq 19), whereas with Ph_3SnH both reactions are competitive and the percentage of alcohol increases as the concentration of the tin hydride is increased. The observation that alcohol is obtained from **Id** but not from **Ia-b** suggests that the cleavage of the ketyl radical anion of **Id** is much slower than that of **Ia-b**. Experimentally it was found that the radical anion of **Id** cleaves about 100 times slower than the radical anion of **Ia** (see Chapter 5).

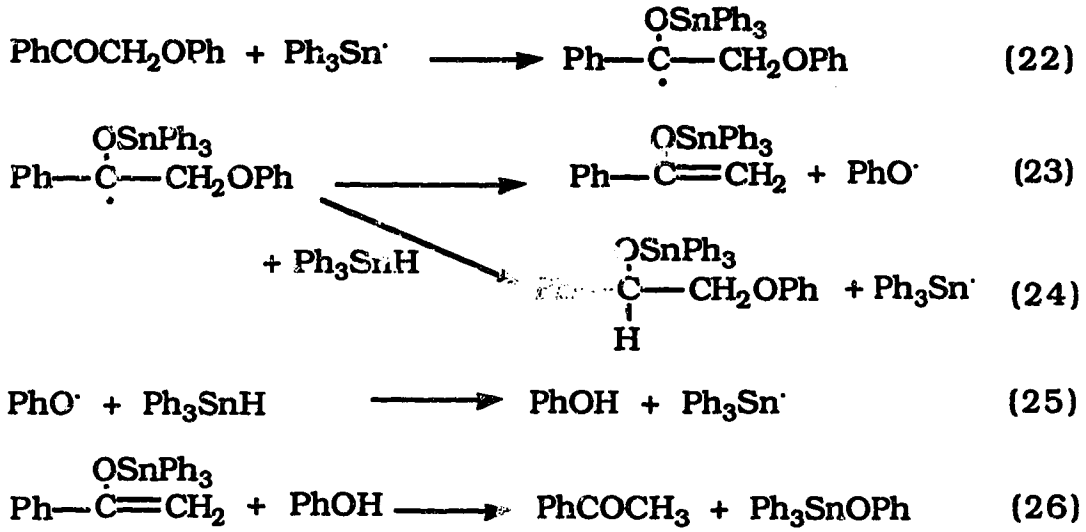


ZH = DMBI, $k_f >> k_H[ZH]$

ZH = Ph_3SnH, $k_f \sim k_H[ZH]$

Scheme IV-4. The ET Mechanisms for the Free Radical Chain Reduction of α-Phenoxyacetophenone

Although the ET mechanism (eq 18-21, Scheme IV-4) could rationalize the experimental results of the reduction of **Id** by both DMBI and Ph_3SnH, an alternative radical addition process must be considered for the Ph_3SnH reduction of **Id** (eq 22-26). The same



product, an alkoxystannane ($PhCH(OSnPh_3)CH_2OPh$), could be formed by either an ET hydrogen abstraction sequence (eq 18 and 20) or an addition hydrogen abstraction sequence (eq 22 and 24). Therefore a product study cannot be used to distinguish between the two sequences. A similar mechanistic consideration has been given for the Ph_3SnH reduction of $PhCOCF_3$.[6a] A thermodynamic approach, discussed in detail for the tin hydride reduction of nitroalkanes,[23] can provide an insight into the viability of the ET from $Ph_3Sn\cdot$ to **Id**. The required standard reduction potential of **Id**, however, is not available.

Therefore the ET and addition mechanisms for the formation of the alcohol ($PhCHOHCH_2OPh$) from the tin hydride reduction of **Id** cannot be distiguished from the available experimental results.

The radical addition mechanism (eq 22, 23, 25, and 26) in principle can also account for the formation of acetophenone. The intermediate α-alkoxylalkyl radical ($Ph\dot{C}(OSnPh_3)CH_2OPh$) undergoes competitive hydrogen abstraction (eq 24) and β-cleavage to give tin enolate ($Ph(OSnPh_3)CH{=}CH_2$) and PhO· radical (eq 23). PhO· abstracts a hydrogen from Ph_3SnH to form PhOH and Ph_3Sn· (eq 25). The protonation of the tin enolate ($Ph(OSnPh_3)CH{=}CH_2$) by PhOH yields acetophenone (eq 26).[24] The formation of a PhO· radical from the β-cleavage of an substituted alkyl radical is extremely rare.[25] Although the sequence (eq 22, 23, 25, and 26) is possible, its viability still needs to be substantiated. Since the Ph_3SnH reduction of $PhCOCH_2F$[6a] and $PhCOCH_2OCOR$ (this work) to $PhCOCH_3$ has been shown to proceed by an ET process, it is reasonable to assume that the Ph_3SnH reduction of a structurally analogous ketone, **Id** ($PhCOCH_2OPh$), to $PhCOCH_3$ proceeds by the same ET process (eq 18, 19, and 21, Scheme IV-4) rather than by the addition process (eq 22, 23, 25, and 26).

3. The Reduction of α-Arylsulfonyl or α-Phenylthio Ketones (Ie-f, II, III)

The AIBN initiated reduction of α-sulfonyl and α-phenylthio ketones (**Ie-f, II, III**) by Ph_3SnH and DMBI yielded only desulfurated products (reactions 6-13, Table IV-1). Except for the reaction of the tertiary sulfone (**III**) with DMBI, all the reactions proceeded readily to give the reduction products in high yields. The lack of the reactivity of the tertiary substrate **III** towards DMBI, previously observed in the reduction of the tertiary α-haloisobutyrophenones by DMBI (see Chapter 2), could be explained by an ET hydrogen abstraction chain sequence (Scheme IV-5).

initiation

$$\text{AIBN} \longrightarrow (CH_3)_2\dot{C}CN \qquad (2)$$

$$(CH_3)_2\dot{C}CN + ZH \longrightarrow (CH_3)_2CHCN + Z^{\cdot} \qquad (3)$$

propagation

$$PhCOCR^1R^2Y + Z^{\cdot} \longrightarrow PhCOCR^1R^2Y^{\cdot -} + Z^{+} \qquad (27)$$

$$PhCOCR^1R^2Y^{\cdot -} \longrightarrow PhCOCR^1R^{2\cdot} + Y^{-} \qquad (28)$$

$$PhCOCR^1R^{2\cdot} + ZH \longrightarrow PhCOCR^1R^2H + Z^{\cdot} \qquad (29)$$

R^1, R^2 = H, CH_3; ZH = DMBI; Y = $ArSO_2$, PhS

Scheme IV-5. The ET Chain Mechanism for the DMBI Reduction of α-Sulfonyl or α-Phenylthio Ketones

For the DMBI reduction of **III** the hydrogen abstraction by the stable tertiary radical ($PhCOCMe_2\cdot$) from DMBI (eq 29, Scheme IV-5)

is too slow to carry the chain efficiently. Since it has been shown in Chapter 2 that the reduction of α-haloisobutyrophenones by DMBI can be promoted by a radical chain transfer agent, PhSH, the effect of PhSH on the reduction of two tertiary substrates, $PhCOCMe_2SO_2Tol$-*p* (III) and $PhCOCMe_2SPh$ (IV), was studied. The results of these studies are listed in Table IV-3.

Table IV-3. The PhSH Promoted Reduction of $PhCOCMe_2SO_2Tol$-*p* (III) and $PhCOCMe_2SPh$ (IV) by DMBI

Reaction	Substrate	Conditions [a]	Product (%) $PhCOCHMe_2$
10	III	60 h, 5% AIBN [b]	16.0
18		43 h, 6 eq PhSH, 5% AIBN	94.1
19	IV	45 h, 2% AIBN	4.4
20		45 h, 2 eq PhSH, 8% AIBN	61.4

[a] 2 eq of DMBI were used in all reactions except where specified. The reactions were carried out in THF at 61 °C. [substrate] = 0.05 M.
[b] 1.2 eq of DMBI were used.

Based on a comparison of the product ($PhCOCHMe_2$) yield (reactions 10 and 18; 19 and 20, Table IV-3), it is apparent that the free radical chain reduction of III and IV is promoted by PhSH. These results are consistent with the ET free radical chain mechanism shown in Scheme IV-6. The hydrogen abstraction of $PhCOCMe_2\cdot$ from PhSH occurs readily to give $PhCOCHMe_2$ and PhS· (eq 30). PhSH is

regenerated through the hydrogen abstraction of DMBI by PhS· (eq 31).

$$PhCOCMe_2^{\cdot} + PhSH \longrightarrow PhCOCMe_2H + PhS^{\cdot} \quad (30)$$

$$ZH + PhS^{\cdot} \rightleftharpoons Z^{\cdot} + PhSH \quad (31)$$

$$PhCOCMe_2Y + Z^{\cdot} \longrightarrow PhCOCMe_2Y^{-\cdot} + Z^{+} \quad (32)$$

$$PhCOCMe_2Y^{-\cdot} \longrightarrow PhCOCMe_2^{\cdot} + Y^{-} \quad (33)$$

ZH = DMBI; Y = $ArSO_2$, PhS

Scheme IV-6. The PhSH Promoted DMBI Reduction of III and IV

The results of the DMBI reduction of **III** and **IV** support the proposal[15a] that the radical anion of **III** and **IV** cleaves to give an enolyl radical and an anion (eq 33, Scheme IV-6). α-Phenylthio ketone radical anions were proposed to undergo cleavage to give an enolate ion and a thiyl radical (eq 34).[26-27] The main argument for this mode of ketyl cleavage is that the dimeric product ($PhCOCH_2CH_2COPh$)

$$Ph-\overset{\overset{O^{-}}{|}}{\underset{\cdot}{C}}-CH_2SPh \longrightarrow PhCOCH_2^{-} + PhS^{\cdot} \quad (34)$$

derived from the enolyl radical was not observed.[27] This suggestion is not consistent with our experimental results. If the enolate ion was formed as an intermediate during the DMBI reduction of $PhCOCH_2SPh$ and $PhCOCMe_2SPh$, the free radical chain reduction would proceed by the sequence shown in Scheme IV-7. According to this mechanism,

$$PhCOCR^1R^2SPh + Z^{\cdot} \longrightarrow PhCOCR^1R^2SPh^{-\cdot} + Z^+ \quad (35)$$

$$PhCOCR^1R^2SPh^{-\cdot} \longrightarrow PhCOCR^1R^{2\,-} + PhS^{\cdot} \quad (36)$$

$$PhS^{\cdot} + ZH \longrightarrow PhSH + Z^{\cdot} \quad (31)$$

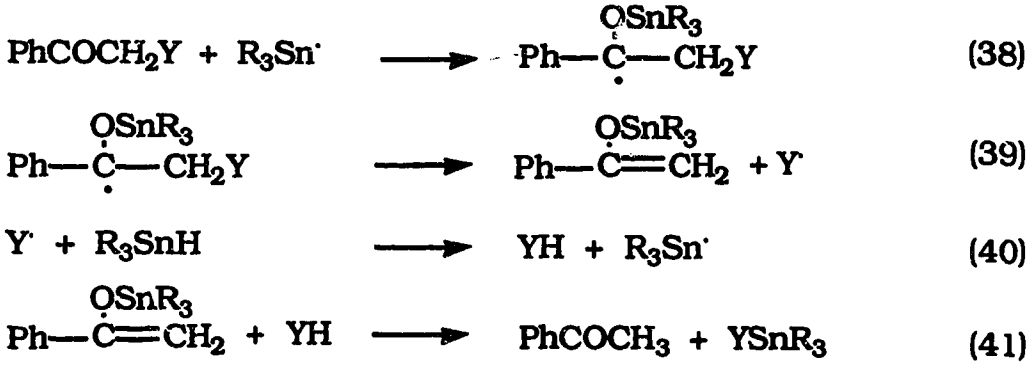
$$PhCOCR^1R^{2\,-} + PhSH \longrightarrow PhCOCR^1R^2H + PhS^- \quad (37)$$

R^1, R^2 = H, CH_3; ZH = DMBI

Scheme IV-7

the tertiary sulfide **IV** would react with DMBI as readily as the primary sulfide **If**, but experimentally it was found that **IV** is much less reactive than **If** towards DMBI reduction. This mechanism cannot explain the acceleration of the reduction of **IV** by PhSH. The proposed mode of the ketyl cleavage (eq 34), therefore, seems unlikely.

As in the reduction of $PhCOCH_2OCOR$ by Ph_3SnH, several mechanisms are possible for the free radical chain reduction of α-sulfonyl and α-phenylthio ketones (**Ie-f, II, III**) by tin hydride. Since the tin hydride reduction of $PhCOCH_2F$, $PhCOCH_2OCOR$, and $PhCOCH_2OPh$ has been shown to proceed by an ET hydrogen abstraction mechanism, a similar chain sequence (Scheme IV-5, ZH = Ph_3SnH) is also possible for the tin hydride reduction of **Ie-f, II,** and **III**. Ueno[28] proposed an addition elimination mechanism for the Bu_3SnH reduction of α-arylsulfonyl and α-phenylthio ketones (Scheme IV-8). The key argument for this mechanism is based on the



Y = PhS, $ArSO_2$; R = Bu, Ph

Scheme IV-8. The Addition Elimination Mechanism for the Tin Hydride Reduction of Ie-f

assumption that α-arylsulfonyl and α-phenylthio ketones react with tin hydride by the same mechanism as allyl sulfones and sulfides. An S_H2 mechanism was proposed for the Bu_3SnH reduction of α-phenylthio ketones (eq 42-43).[29] Because of the mechanistic diversity of the tin

$$PhCOCH_2SPh + R_3Sn^{\cdot} \longrightarrow PhCOCH_2^{\cdot} + PhSSnR_3 \qquad (42)$$

$$PhCOCH_2^{\cdot} + R_3SnH \longrightarrow PhCOCH_3 + R_3Sn^{\cdot} \qquad (43)$$

hydride reduction of α-arylsulfonyl and α-phenylthio ketones, more investigation is required before any definitive mechanistic conclusions can be drawn.

After the completion of the above work it was reported that aliphatic α-phenylsulfonyl ketones can be readily desulfonylated with excess tributyltin hydride and AIBN (2 equivalents) in refluxing toluene.[30] The reduction, however, did not proceed readily for aromatic ketones. This order of reactivity (aliphatic ketones > aromatic ketones) is the opposite of what we observed. Under the same conditions, the reduction of 1-(phenylsulfonyl)-2-nonanone by Ph_3SnH gave 57.4 % of 2-nonanone, but the reduction of **Ie** gave 94% of acetophenone. We can offer no explaination for this difference in the reactivity order.

Conclusions

α-Substituted acetophenones ($PhCOCH_2Y$, Y = OCOPh, $OCOCH_3$, OPh, SO_2Tol-*p*, SPh), **Ia-f**, react with DMBI in the presence of AIBN to yield acetophenone by an ET chain sequence (eq 1-6, Scheme IV-1). These ketones are suitable electron acceptors and the ketyls cleave readily to give an enolyl radical ($PhCOCH_2\cdot$) and an anion (Y^-). The secondary and tertiary α-substituted ketones, **II**, **III**, and **IV**, also react similarly with DMBI to give the corresponding ketones. These results suggest that a change in the leaving group (Y) does not change the reaction pattern of the α-substituted acetophenones with DMBI. The reactivity of the ketones, however, is controlled by the leaving group. Qualitatitively, $PhCOCH_2OPh$ is less reactive than the rest of the substituted acetophenones studied ($PhCOCH_2Y$, Y = OCOPh, SPh, Tol-*p*). The relative ET reactivity of α-substituted acetophenones can therefore be changed by the appropriate selection of the α-substituent (Y). As originally suggested in the introduction, these ketones are useful probes for ET reactions.

The reduction of **Ia-f** by Ph_3SnH was compared to the reduction by DMBI. The reaction of **Ia-d** with tin hydride proceeds via an ET chain sequence, whereas the mechanism for the free radical chain reduction of **Ie-f** is not clear. The results of this chapter also suggest the possibility that DMBI and Ph_3SnH can serve as selective reducing agents for α-carbonyloxy, α-arylsulfonyl, and α-phenylthio ketones.

Experimental

1. Materials

The preparation or purification of **DMBI**, **AIBN**, **acetophenone**, **α-fluoroacetophenone**, **1-phenyl-2-octanone**, ***p*-di-*tert*-butylbenzene**, **benzene**, **α-(phenylthio)isobutyrophenone (IV)**, and **THF** has been described in Chapter 2. **Triphenyltin hydride** (Aldrich) was used as supplied.

α-(Benzoyloxy)acetophenone (Ia) was prepared according to the literature procedure,[31] mp 119-119.8 °C (lit.[31] 119-121 °C); ^{1}H NMR δ 5.62 (s, 2 H), 7.42-7.7 (m, 6 H), 8.0-8.2 (m, 4 H).

α-(Acetoxy)acetophenone (Ib) was prepared according to the literature procedure,[32] mp 48-9 °C (lit.[33] 49 °C); ^{1}H NMR δ 2.25 (s, 3 H), 5.39 (s, 2 H), 7.45-8.0 (m, 5 H).

α-(2',4',6'-Trimethylbenzoyloxy)acetophenone (Ic) was prepared according to Ono's general method for the preparation of esters,[34] mp 79-80.5 °C; ^{1}H NMR δ 2.3 (s,3 H), 2.45 (s, 6 H), 5.6 (s, 2 H), 7.5-8.0 (m, 5 H). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.58; H, 6.43. Found: C, 76.68; H, 6.51.

α-(Phenoxy)acetophenone (Id) was synthesized using the same procedure as was used to synthesize **Ic**, mp 72-72.5 °C (lit.[35] 71-72 °C); ^{1}H NMR δ 5.3 (s, 2 H), 7.0-8.1 (m, 10 H).

2-Phenoxy-1-phenyl-1-ethanol was prepared through the reduction of **Id** with sodium borohydride, mp 62.0-62.8 °C (lit.[35] 63-64 °C); ^{1}H NMR δ 3.3 (bs, 1 H), 4.3 (m, 2 H), 5.35 (dd, 1 H, J = 7.5 Hz), 7.1-7.7

(m,10 H). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.58. Found: C, 78.17; H, 6.79.

α-(*p*-Methylbenzenesulfonyl)acetophenone (Ie) was made according to the literature procedure,[36] mp 108-9 °C (lit.[36] 109-109.5 °C); ^{1}H NMR δ 2.4 (s, 3 H), 4.7 (s, 2 H), 7.3-8.0 (m, 9 H). Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.68; H, 5.14; S, 11.69. Found: C, 65.93; H, 5.20; S, 11.55.

α-(Phenylthio)acetophenone (If) was synthesized according to Ono's general procedure for the preparation of sulfides,[37] mp 51-52 °C (lit.[38] 49 °C); ^{1}H NMR δ 4.2 (s, 2 H), 7.2 (m, 8 H), 7.8 (m, 2 H).

α-(*p*-Methylbenzenesulfonyl)propiophenone (II) was made according to Ono's general procedure for the alkylation of active methylene compounds.[39] A solution of **Ie** (2.74 g, 10 mmol), methyl iodide (1.42 g, 10 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.52 g, 10 mmol) in a mixture of benzene (20 mL) and DMF (4 mL) was stirred at room temperature for 24 h. It was filtered, and the filtrate was washed with water (3 x 20 mL) and dried over anhydrous magnesium sulfate. After the evaporation of benzene, the residue was recrystallized from ethanol to give white crystals, mp 97-98 °C; ^{1}H NMR δ 1.6 (d, 3 H, J = 7.5 Hz), 2.49 (s, 3 H), 5.2 (q, 1 H, J = 7.5 Hz), 7.3-8.0 (m, 9 H). Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.75; H, 5.59; S, 11.12. Found: C, 66.40; H, 5.67; S, 10.99.

α-(*p*-Methylbenzenesulfonyl)isobutyrophenone (III) was made according to Ono's general procedure for the alkylation of active methylene compounds.[39] A solution of **Ie** (2.74 g, 10 mmol), DBU (3.34 g, 22 mmol) and methyl iodide (3.55 g, 25 mmol) in DMF (10

mL) was heated at 70 °C for 0.5 h. During this period more methyl iodide (2.84 g, 20 mmol) was added. After the mixture was cooled to room temperature it was was poured into ice-water (100 mL). The yellow precipitate formed was filtered, washed with water and recrystallized from ethanol several times to give white crystals, mp 51-53 °C (lit.[40] 48-53 °C; lit.[41] 50.5-51.5 °C); ^{1}H NMR δ 1.75 (s, 6 H), 2.5 (s, 3 H), 7.3-8.0 (9 H). **III** was also prepared from the reaction of α-bromoisobutyrophenone with sodium *p*-tolylsulfinate (*p*-TolSO$_2^-$) in DMF at room temperature,[40] mp 52-53 °C.

1-(Phenylsulfonyl)-2-nonanone was prepared according to the literature procedure,[42] mp 55-56 °C; ^{1}H NMR δ 0.85 (t, 3 H), 1.3 (bs, 10 H), 1.55 (m, 2 H), 2.7 (t, 2 H, *J* = 7.5 Hz), 4.15 (s, 2 H), 7.5-7.7 (m, 3 H), 7.9 (d, 2 H). Anal. Calcd for $C_{15}H_{22}O_3S$: C, 63.80; H, 7.86. Found: C, 63.96; H, 7.83.

2. Methods and Procedures

Measurements of physical constants, microanalyses, spectral measurements, and GC analyses were carried out using the same instrumentation described in Chapter 2.

In all cases a stainless steel column (10 ft x 1/8 in.) packed with 5% OV-101 on Chromosorb WAW DMCS 100/200 mesh was used for the quantitative GC analysis. A stainless steel column (10 ft x 1/8 in.) packed with 5% FFAP on Chromosorb WAW DMCS 60/80 mesh was used to determine the presence or absence of α-methylbenzylalcohol

($PhCHOHCH_3$). ^1H NMR was used to detect the presence of the alcohol ($PhCHOHCH_2X$) in the reaction mixture.

General Procedure for the Reduction. An aliquot of the substrate (0.05 M), the reducing agent (0.06 M), the internal standard (*p*-di-*tert*-butylbenzene, 0.02 M), and AIBN (0.0025 M) was placed in a pyrex ampule. The ampule was degassed and sealed using the standard high vacuum procedure, and thermostated at 61 °C for the specified time. The ampule was opened and analyzed by GC. For each reaction the products were identified by the comparison of their GC retention times, GC-IR spectra and GC-MS spectra with those of authentic samples. All reactions were run in duplicate and the average yield of the products is shown in Table IV-1.

The Competitive Reduction of Ia to Ic. The relative rate constants for the reaction of **Ic** and **Ia** with DMBI and Ph_3SnH were calculated using the Ingold-Shaw equation.[43] The disapperance of the starting substrates was monitored by GC. The detailed procedure for the calculations has been described in Chapter 2. An aliquot solution of **Ia** (0.05 M), **Ic** (0.05 M), AIBN (0.0025 M), the internal standard (0.025M), and the reducing agent (< 0.05 M) was placed in a pyrex tube, degassed, sealed, and thermostated at 61 °C for 57 h. The reduction mixture was analyzed by GC on the OV-101 column to obtain the final concentrations of **Ia** and **Ic**.

General Procedure for Trapping Experiments. An aliquot solution of α-substituted acetophenones (0.02 M), the internal standard (0.005 M), AIBN (0.001 M), and the reducing agent (0.01 M) in 1-hexene (containing 10-20% of benzene to dissolve the substrate)

was used. The general procedure for the reduction was followed. The products were analyzed on the OV-101 column and characterized by GC-IR and GC-MS.

Analysis of the Ph_3SnH Reduction Products of Id. The general procedure for the reduction was followed. After the reaction the solvent was removed using a water aspirator. The residue was dissolved in $CDCl_3$, and its ^1H NMR spectrum was run. The integration of the methyl protons in acetophenone, the methylene protons in **Id**, and the methylene protons in the alcohol ($PhCHOHCH_2OPh$) was measured. The integration ratio of the reduction products relative to the internal standard was compared with that of a standard solution of products with known concentrations. An equation similar to the one described in Chapter 2 for the GC analysis was used.

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CHAPTER 5

New Ketone Fragmentation Probes and Measurements of Ketyl Cleavage Rate Constants

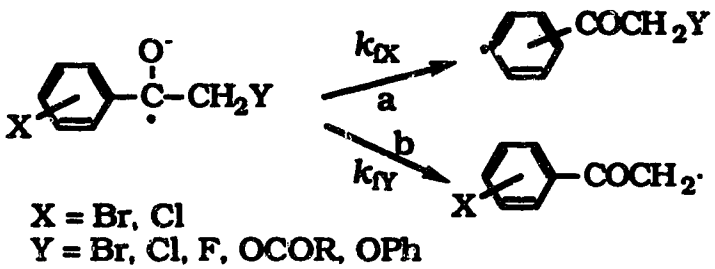
Introduction

α-Haloacetophenones have been used as chemical probes to distinguish between the ET hydrogen atom abstraction and the hydride transfer mechanisms in the reduction of ketones by several hydride equivalents.[1] In Chapter 4 other α-substituted acetophenones ($PhCOCH_2Y$, Y = OCOR, OPh, SO_2Ar, SPh) were also shown to be useful as ketone fragmentation probes. The mechanistic differentiation is based on the study of the products (see Chapter 4).

In this chapter, an intramolecular competitive method was developed to measure the ketyl cleavage rate constants of a series of α-substituted acetophenones ($PhCOCH_2Y$, Y = Br, Cl, F, OCOR, OPh). Recently the fragmentation rate constants (k_{fX}) of a number of ring halogenated acetophenone and benzophenone ketyls (eq 1) have been reported.[2-4] If one assumes that substitution at the α-position of acetophenone does not affect the cleavage rate of a ring halogenated acetophenone ketyl (k_{fX}), then the ET reduction of acetophenones that are both ring substituted and α-substituted will undergo competitive fragmentation reactions (eq 2). A determination of the product ratio resulting from these competitive fragmentations allows a series of rate constants to be determined for the α-substituent (k_{fY}).

(1)

X = Br, Cl
R = Ph, CH_3



(2)

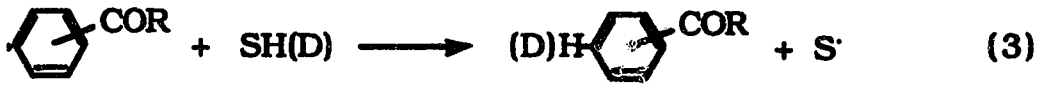
X = Br, Cl
Y = Br, Cl, F, OCOR, OPh

Results and Discussion

The structure and the numbering of compounds studied in this chapter are shown in Chart V-1.

1. Ring Halogenated Arylketones (Ia-g and IIa-b) as Ketone Fragmentation Probes for ET Reactions

The radical anions of ring halogenated acetophenones (I) and ring halogenated benzophenones (II) cleave to give aryl radicals and halide ions.[2-4] The aryl radical formed can undergo hydrogen abstraction from various reagents and from solvents[5] to form the dehalogenated ketone. The intermediacy of the aryl radical in the formation of the dehalogenated ketones can be substantiated by appropriate deuterium incorporation experiments (eq 3).[5a] The ring halogenated arylketones



(3)

Chart V-1. The Structure and Numbering of Compounds Studied

$XC_6H_4COCH_3$

Ia-h

a, X = *o*-Br

b, X = *p*-Br

c, X = *m*-Br

d, X = *o*-Cl

e, X = *m*-Cl

f, X = *p*-Cl

g, X = *p*-I

h, X = *m*-I

XC_6H_4COAr

IIa-b

a, X = *p*-Br,
Ar = Ph

b, X = *p*-Br
Ar = Mes

$XC_6H_4COCH_2Y$

IIIa-k

a, X = *p*-Br, Y = Br

b, X = *p*-Br, Y = Cl

c, X = *p*-Br, Y = F

d, X = *p*-Br, Y = OCOPh

e, X = *p*-Br, Y = OPh

f, X = *p*-Br, Y = $OCOCH_3$

g, X = *o*-Cl, Y = OPh

h, X = *o*-Br, Y = F

i, X = *o*-Br, Y = OCOPh

j, X = *p*-I, Y = OCOPh

k, X =*m*-I, Y = OCOPh

$PhCOCH_2Y$

IVa-f

a, Y = Br

b, Y = Cl

c, Y = F

d, Y = OCOPh

e, Y = OPh

f, Y = $OCOCH_3$

$XC_6H_4COCH{=}CHPh$

Va-b

a, X = *p*-Br

b, X = *o*-Br

PhCOCH=CHPh

VI

$XC_6H_4COCH_2CH_2Ph$

VIIa-b

a, X = *p*-Br

b, X = *o*-Br

(I and II) can therefore be used as ketone fragmentation probes to differentiate between the ET and the polar ionic mechanisms for the reaction of ketones with a nucleophile (Nu^-), since the dehalogenated ketone is the product of the ET process and the halogenated alcohol ($XC_6H_4CNuOHR$) is the product of the polar mechanism.

The reaction of I and II with DMBI was used as a model for the study of the ET reactivities. The reactions were carried out at 61 °C in acetonitrile (AN). The results of these reactions, together with the reported reduction potentials (E^o) of the haloketones and the ketyl cleavage rate constants (k_f), are listed in Table V-1.

For the haloketones studied, in the absence of radical initiators there was little if any reaction (< 2%) (see reactions 2, 4, 6, 10 and 12). All the reactions could be initiated (5% AIBN) and gave the corresponding dehalogenated ketones. No alcohol (XC_6H_4CHOHR, R = Me, Ph; X = Cl, Br, I) was observed. These results clearly establish that I and II are reduced by DMBI via a free radical chain sequence.

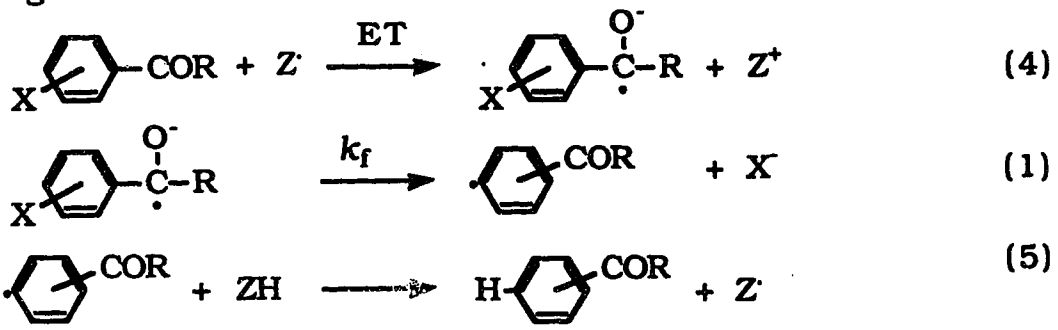
In order to study the possibilty of a direct halogen atom transfer step in the free radical chain reduction, the competitive rate of the reduction of *p*-iodoacetophenone (**Ig**) and *p*-bromoacetophenone (**Ib**) (k_{Ig}/k_{Ib}) was determined (see the experimental section). The relatively small value of k_{Ig}/k_{Ib} (3.0 ± 0.6) excludes the possibity of the direct halogen atom transfer step in the free radical chain reduction of haloacetophenones by DMBI. The latter mechanism would require a much larger reactivity difference between aryl iodides and aryl bromides.[6] The ET free radical chain mechanism (Scheme V-1) is therefore suggested for the reduction of these haloketones.

Table V-1. The Reduction of the Haloacetophenones (Ia-g) and Halobenzophenones (IIa-b) by DMBI [a]

Rt. No.	ArX (I-II)	Additive	Product (%) [b] ArH	ArX	E^o (V) [c]	k_f (s^{-1}) [d]
1	**Ia**	AIBN (5%)	80.6 ± 0.4	19.8 ± 0.2	- [g]	- [g]
2	**Ib**	-	0.2 ± 0.2	94.3 ± 1.7	> -2.08	> 8 x 10^6
3		AIBN (5%)	70.4 ± 0.9 [e]	31.5 ± 0.6		
4	**Ic**	-	-	96.3 ± 2.3	-1.83	8 x 10^3
5		AIBN (3%)	63.3 ± 1.7	39.0 ± 2.8		
6	**Id**	-	-	111.7 ± 9	-1.92	3 x 10^5
7		AIBN (4%)	50.2 ± 3.6	46.8 ± 1.9		
8	**Ie**	AIBN (4%)	0.4 ± 0.1	103.6 ± 4	-1.84	15
9	**If**	AIBN (4%)	17.3 ± 1.7	84.7 ± 3.4	-1.91	3 x 10^3
10	**Ig**	-	0.9	106.3	- [g]	- [g]
11		AIBN (4%)	71.9 ± 2.2	23.2 ± 2.1		
12	**IIa**	-	1.8 ± 0.1	97.8 ± 12.3	-1.79	4 x 10^4
13		AIBN (4%)	70.2 ± 0.5	24.5 ± 1.2		
14	**IIb**	AIBN (5%) [f]	50.4 ± 5.8	56.9 ± 3.9	- [g]	- [g]

[a] All reactions were run in AN at 61 °C for 47 h with [ArX] = [DMBI] = 0.05 M. [b] Average of two runs. [c] The reduction potential of ArX in AN (versus SCE), taken from ref. 3. [d] The cleavage rate constant of $ArX^{-\cdot}$ in AN, taken from ref. 3. [e] When the reaction was carried out in CD_3CN in the presence of 7% AIBN the acetophenone (42.5 ± 2.5%) was found to be 5 ± 2% monodeuterated. [f] 60 h. [g] unknown.

propagation

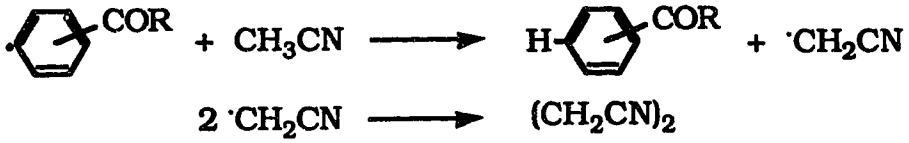


(4)

(1)

(5)

termination



(6)

R = CH_3, Ph, 2,4,6-$Me_3C_6H_2$

ZH = DMBI; X = I, Br, Cl

Scheme V-1. The ET Free Radical Chain Mechanism for the Reduction of Ring Halogenated Arylketones I and II by DMBI

From the qualitative comparison of the product yield in the AIBN initiated reduction of **Ia-g** (reactions 1-11, Table V-1), it is apparent that the chloroacetophenones (**Id-f**) are less reactive than the bromoacetophenones (**Ia-c**), and that the difference in their reactivity within the chloride series is much more pronounced than the difference within the bromide series. The order of reactivity in the chloride series is: *o*-Cl > *p*-Cl > *m*-Cl.

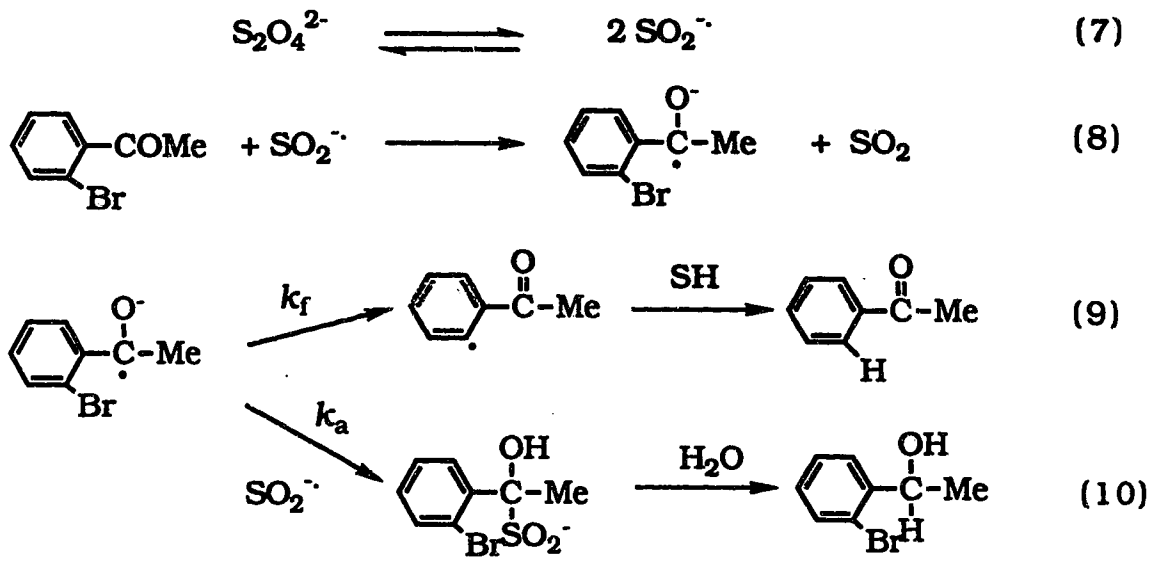
The AIBN initiated reduction of *p*-bromobenzophenone (**IIa**) and *p*-bromophenyl mesityl ketone (**IIb**) by DMBI also gave the corresponding debrominated ketones in moderate yields (reaction 13-14, Table V-1). Despite the fact that **IIb** is thought to be sterically more hindered than **IIa** for reactions which involve carbonyl additions, electron transfer reactions do not seem to be subject to this type of steric hindrance.[7] In support of this argument **IIb** was found to be slightly more reactive than **IIa** towards DMBI reduction. The competitive rate of the reduction of **IIa** to **IIb** (k_{IIa}/k_{IIb}) was determined to be 0.44 ± 0.02 (see the experimental section).

To illustrate the potential application of the ring halogenated arylketones as mechanistic probes for ET reactions, the reaction of *o*-bromoacetophenone (**Ia**) with sodium dithionite was studied.

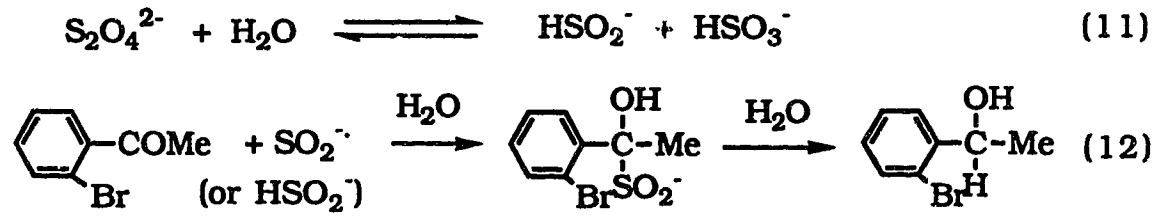
The reduction of carbonyl compounds by sodium dithionite has been extensively investigated.[8] A mechanistic sequence involving an ET reaction between $SO_2^{-\cdot}$ and ketones, followed by the coupling of the ketyl with $SO_2^{-\cdot}$, was suggested.[9] If the ketyl intermediate was involved in the sodium dithionite reduction of *o*-bromoacetophenone (**Ia**), the debominated products ($PhCOCH_3$ or its reduction product, $PhCHOHCH_3$) would be formed from the ketyl cleavage of **Ia** (eq 9, Scheme V-2).

The reduction of **Ia** (0.1 M) with sodium dithionite (0.5 M) in DMF/H_2O (1/2) at 100 °C gave 93% of the corresponding alcohol (o-$BrC_6H_4CHOHCH_3$). No debrominated products (< 0.05%, $PhCOCH_3$ or $PhCHOHCH_3$) were detected by GC-MS and GC-IR. The GC-IR can detect at least 0.05% of the debrominated products (see the

a. The ET Mechanism:



b. The Nucleophilic Addition Mechanism:



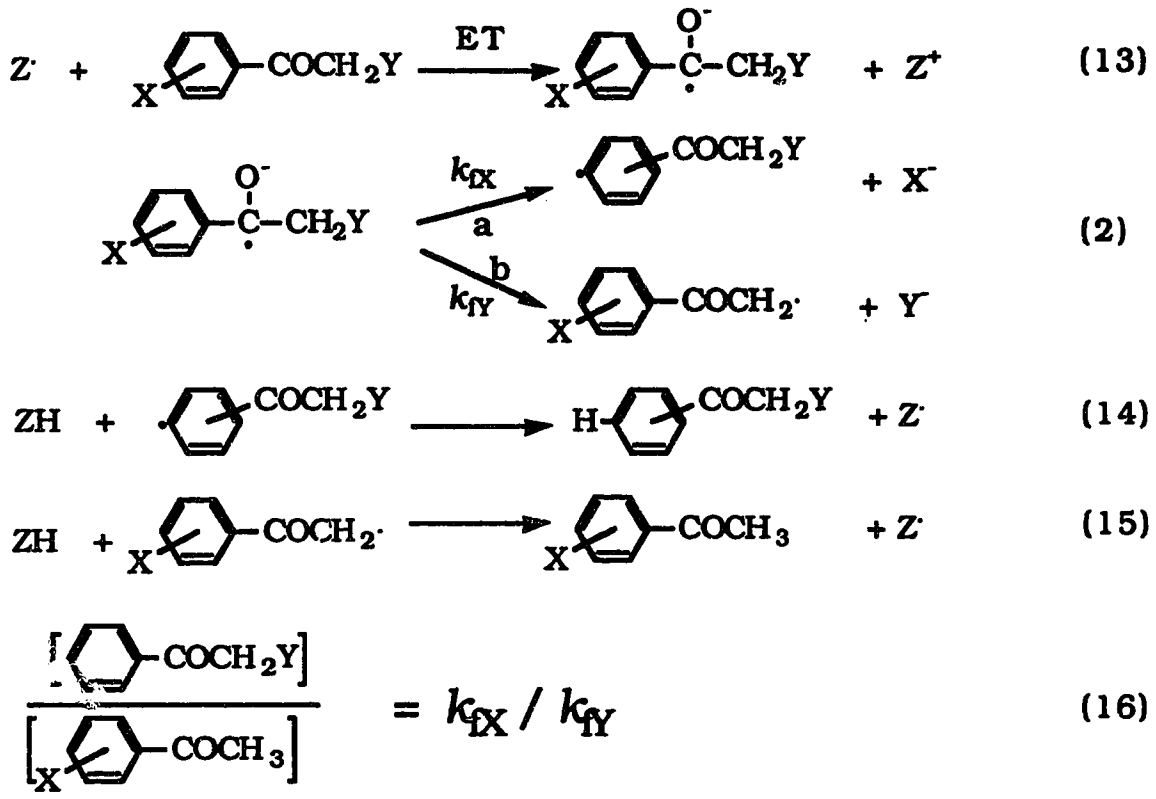
Scheme V-2. Possible Mechanisms for the Reduction of *o*-Bromoacetophenone by $Na_2S_2O_4$

experimental section). The ET mechanism (Scheme V-2a) requires that $k_a[SO_2^{-\cdot}]/k_f > 93/0.05 = 1860$. The *o*-bromoacetophenone ketyl cleaves to give the bromide ion and the aryl radical (eq 9) with k_f = $9 \times 10^3 - 5 \times 10^5$ s^{-1} in aqeuous solution.[10] Assuming that the

combination of $SO_2^{-\cdot}$ and the ketyl (k_a) proceeds at a rate of 1 x 10^9 M^{-1} s^{-1},[11] the ET radical combination mechanism requires [$SO_2^{-\cdot}$] > 0.017 - 0.93 M. It is unreasonable for $SO_2^{-\cdot}$ to exist in the solution of sodium dithionite (0.5 M) at such high concentrations.[12] The ET radical recombination sequence (Scheme V-2a) is therefore unlikely for the reaction of **Ia** with $S_2O_4^{2-}$. The previously proposed[13-14] nucleophilic addition of SO_2^{2-} or its equivalents, $SO_2^{-\cdot}$ or HSO_2^- to the carbonyl to give the α-hydroxy-sulfinate (eq 12) is, therefore, more likely.

2. Cleavage Rate Constants of α-Substituted Acetophenone Radical Anions Calibrated by an ET Clock

If the substitution at the α-position of acetophenone does not affect the cleavage rate of a ring halogenated acetophenone (**Ia-g**) ketyl, then the radical anion of an acetophenone ($XC_6H_4COCH_2Y$, **III**, X = Br, Cl, I; Y = Br, Cl, F, OCOR, OPh) that is both ring substituted and α-substituted will undergo competitive fragmentation reactions to give an aryl radical or an enolyl radical (eq 2). The hydrogen abstraction by these radicals yields an α-substituted acetophenone ($PhCOCH_2Y$, **IV**) and a ring halogenated acetophenone ($XC_6H_4COCH_3$, **I**) (eq 14-15). A determination of the ratio of these two products resulting from the competitive ET reduction of **III** allows a series of rate constants (k_{fY}) to be determined for α-substituents from the known k_{fX}, see Scheme V-3.



Scheme V-3. The Competitive ET Reduction of the Disubstituted Acetophenones (IIIa-k) by DMBI

The ketyl cleavage of *p*-bromoacetophenone was used as an ET clock (k_{fX}, Scheme V-3) for the calibration of the cleavage rate constants of α-substituted acetophenones (k_{fY}). The electrochemically measured fragmentation rate constants of *p*-bromoacetophenone ketyl are almost the same in both AN and DMF (k_f: AN[3] > 8 x 10^6 s^{-1}; DMF[4] 3.2 x 10^7 s^{-1}). This observation is not surprising since the solvation

energy for the bromide ion in both solvents is nearly the same (ΔG_t^o < 1.2 kcal/mol)[15]. A similar observation was made for the fragmentation rate constants obtained from the electrochemical reduction of *p,p'*-dibromobenzophenone in these two solvents ($k_{f(DMF)}/k_{f(AN)}$ = 1.04).[16] The fragmentation rate in DMF, k_f, was determined by a homogeneous redox catalysis method, which is potentially more accurate for very fast reactions. This value was therefore used as a standard in the calculation of the cleavage rate constants, k_{fX} or k_{fY}, determined from the competitive reductions carried out in AN.

DMBI was used as the reducing agent, ZH (Scheme V-3). Its reaction with haloacetophenones and α-substituted acetophenones has been shown, in this chapter and in Chapters 2 and 4, to proceed by the ET chain mechanism. The reductions were carried out in acetonitrile (AN) at 23 °C, 61 °C, and 90 °C. In all cases the free radical chain mechanism was confirmed by initiation with AIBN and inhibition with *p*-dinitrobenzene (DNB). Photostimulation of tris(2,2'-bipyridyl)ruthenium (II) diperchlorate, $Ru(bpy)_3(ClO_4)_2$, was used to initiate the chain reaction at 20 °C (vide infra). For comparison, an initiator, di-*tert*-butylperoxyoxalate (DBPO),[17] was also used at room temperature to initiate the free radical chain reduction. The results of the intramolecular competitive reductions of **IIIa-k** are listed in Table V-2. Table V-2 also includes the calculated cleavage rate constants, k_{fY}, using eq 16.

Table V-2. The Intramolecular Competitive Reduction of the Disubstituted Acetophenones (IIIa-k)

Rt.No.	IIIa-k	Reaction conditions [a,b]	Product (%) [c] I	IV	III	k_{IY} [d] or k_{IX} [i] (s^{-1})
15	**IIIa**	23 °C, 20 h	47.8	< 2 [e]	49.5	> 7.8 x 10^8
16		23 °C, 20 h, 2% DNB	3.1	< 2	90.2	
17	**IIIb**	23 °C, 17 h	95.7 ± 0.3	< 0.4 [f]	0.0	> 6.4 x 10^9
18		23 °C, 17 h, 4% DNB	1.9 ± 1.4	< 0.4 [f]	87.6 ± 1.3	
19	**IIIc**	61 °C, 2% AIBN, 53 h	56.7 ± 1.2	0.036 ± 0.006	40.5 ± 1.2	(5.0 ± 1.0) x 10^9
20	**IIId**	61 °C, 3 % AIBN, 48 h	103.8 ± 6	0.76 ± 0.1	1.6 ± 0.4	(4.4 ± 1.3) x 10^9
21		20 °C, 4.7 % DBPO, 48 h	42.3 ± 2.0	0.19 ± 0.04	63.0 ± 8	(7.1 ± 1.8) x 10^9
22	**IIIe**	61 °C, 4% AIBN, 47 h	9.6 ± 0.7	70.9 ± 2.9	20 ± 7	(4.5 ± 0.1) x 10^6
23		23 °C, 5% DBPO, 48 h	1.10 ± 0.1	8.2 ± 0.5	95.1 ± 20	(4.2 ± 0.1) x 10^6
24		20 °C, 3.3% sens.[g], hv [h], 12 h	6.3 ± 0.2	38.8 ± 1.2	62.3 ± 3	(5.1 ± 0.1) x 10^6
25		20 °C, hv [h], 12 h	0.65	1.4	108.4	
26	**IIIf**	23 °C, 4.7% DBPO, 48 h	27.4 ± 5.0	0.7 ± 0.3	63.4 ± 10	(1.2 ± 0.8) x 10^9
27	**IIIg**	20 °C, 1.7% sens.[g], hv [h], 35 h	38.2 ± 3.6	0.6 ± 0.05	41.8 ± 11.1	(19 ± 3.3) x 10^6 [j]
28		20 °C, hv [h], 35 h	1.3	-	96.8	
29	**IIIh**	61 °C, 4% AIBN, 36 h	13.2 ± 0.8	4.8 ± 1.0	65.1 ± 1.6	(1.8 ± 0.8) x 10^9 [i]

Table V-2. -continued

Rt.No.	IIIa-k	Reaction conditions [a,b]	Product (%) [c] I	IV	III	k_{fY} [d] or k_{fX} [i] (s^{-1})
30	IIIh	90 °C, 6% AIBN, 1.5 h	18.6 ± 3.2	7.5 ± 1.0	51.9 ± 0.3	(2.0 ± 1) x 10^9 [i]
31	IIIi	61 °C, 6% AIBN, 72 h	11.5 ± 1.4	9.1 ± 1.0	77.9 ± 9.9	(3.5 ± 1.8) x 10^9 [i]
32		90 °C, 14% AIBN, 2.3 h	12.5 ± 3.6	15.6 ± 1.7	73.7 ± 5	(5.5 ± 3.8) x 10^9 [i]
33		23 °C, 5% DBPO, 48 h	16.6 ± 1.3	13.7 ± 0.9	61.1 ± 5.3	(3.6 ± 1.6) x 10^9 [i]
34		20 °C, 3.4% sens.g, hν [h], 13 h	12.5 ± 1.0	15.7 ± 1.6	65.2 ± 10	(5.5 ± 2.5) x 10^9 [i]
35		20 °C, hν [h], 13 h	3.0 ± 0.1	trace	107 ± 16	
36	IIIj	61 °C, 3% AIBN, 19 h	11 ± 4.3	25.4 ± 6.6	50.5 ± 5.2	(10.5 ± 5) x 10^9 [i]
37	IIIk	61 °C, 4% AIBN, 29 h	32.5 ± 6.6	0.83 ± 0.18	50.5 ± 8.1	(1.1 ± 0.8) x 10^8 [i]

[a] All reactions were carried out in AN in the dark, except where specified in the table, with less than 1 equivalent of DMBI. [b] In the absence of AIBN **IIIc-k** showed little reaction (< 5%). [c] Average of at least two runs. The errors indicated correspond to average deviation from the mean. The structure of the products were shown on Chart V-1. [d] Calculated using k_{fX}(*p*-Br) = 3.2 x 10^7 s^{-1}. [e] The detection limit by GC-IR was > 1 x 10^{-3} M. [f] The detection limit by GC-IR was > 2 x 10^{-4} M. [g] sens.= $Ru(bpy)_3(ClO_4)_2$. [h] A filter solution of $K_2Cr_2O_7$-$NaNO_2$-NaOH[21] was used. The light source was 2 x 200 W incandescent light bulbs. [i] k_{fX} calculated using the measured k_{fY}. [j] Calculated using k_{fX}(*o*-Cl) = 3 x 10^5 s^{-1}.

The temperature dependence of the relative cleavage rates in the initiated reductions was found to be small (compare reactions 20 and 21; 22 and 23; 29 and 30; 31, 32, and 33). It is justified, therefore, to use the electrochemical rates determined at room temperature and the relative cleavage rates (or more precisely the product ratio) determined at 61 °C to calculate the new cleavage rate constants at room temperature.

$Ru(bpy)_3(ClO_4)_2$ was used to photochemically initiate the reduction of **III** at room temperature. In the absence of $Ru(bpy)_3^{2+}$ there is almost no reduction (< 2%) (see reactions 25 and 24; 27 and 28; 34 and 35). The photochemically initiated reduction was also compared with DBPO initiated reductions for several substrates. Both gave essentially the same product ratios (reactions 23 and 24; 33 and 34). These observations indicate that the same ET chain mechanism is involved in the two initiated reductions (Scheme V-3).

The $Ru(bpy)_3^{2+}$ initiated reductions of organic substates by NADH model compounds has been extensively investigated. Kellog reported the photosensitized reduction of α-substituted ketones by 3-methyl-2,3-dihydrobenzothiazoles[18] and 1,4-dihydropyridines.[19] An ET chain sequence involving $Ru(bpy)_3H^{2+}$ was suggested for the reduction. The luminescence of $[Ru(bpy)_3]^{2+*}$ can be quenched by amines[20] and *N*-benzyl-1,4-dihydronicotinamide (BNAH)[21] but not by α-bromo-acetophenone.[22] The quenching rate constant, k_q, by *N*,*N*-dimethyl-aniline (DMA, E^o_{ox} = 0.85V, SCE, AN) and *N*,*N*,*N'*,*N'*-tetramethyl-phenylenediamine (TMPD, E^o_{ox} = 0.15 V, SCE, AN) is 7.1×10^7 and 1.2×10^{10} M^{-1} s^{-1} respectively.[20] DMBI with an oxidation potential of

0.31 V (SCE, AN, see Chapter 2) is therefore expected to quench the excited $[Ru(bpy)_3]^{2+*}$ by an ET reaction with a rate constant ranging from 7.1×10^7 to 1.2×10^{10} M^{-1} s^{-1} to give $DMBI^{+\cdot}$ and $[Ru(bpy)_3]^{+}$. The ET from $[Ru(bpy)_3]^{+}$ (E^o_{ox} = -1.35 V, SCE, AN)[23] to the substrate **III** would initiate the chain reduction.

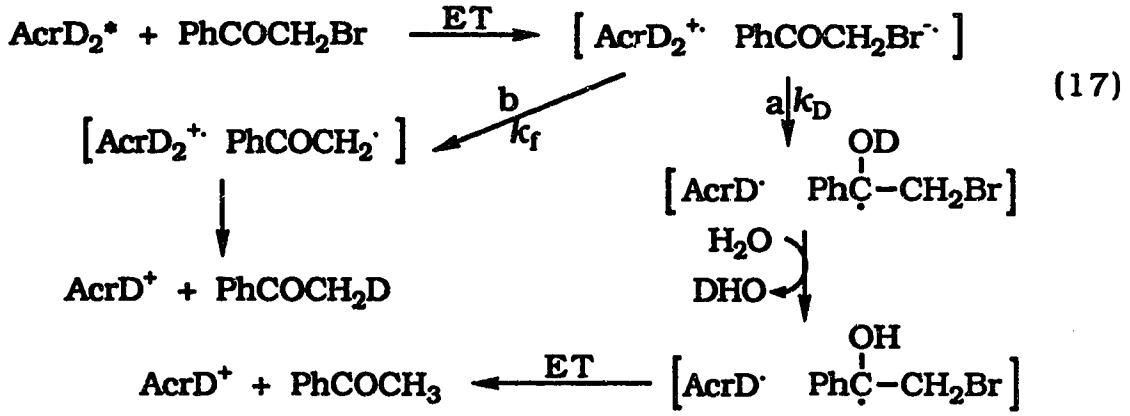
In order to substantiate the validity of the assumption that the fragmentation rate of Y was not appreciably affected by X, or that the fragmentation rate of X was not affected by Y, another determination of the same value (k_{fY}) was carried out using a different substituent X.

The cleavage rate of *o*-chloroacetophenone ketyl anion was reported to be 3×10^5 s^{-1} in AN,[3] and that of *p*-bromoacetophenone was 3.2×10^7 s^{-1} in DMF.[4a] In support of our original assumption, almost the same cleavage rate constant was obtained from the intramolecular reduction of *o*-Cl or *p*-Br and α-OPh (**IIIg** and **IIIe**) with a cleavage rate constant of $(11.8 \pm 7.3) \times 10^6$ s^{-1} for α-OPh, see reactions 24 and 27.

The reduction of *p*-bromophenacyl bromide (**IIIa**) and chloride (**IIIb**) gave only *p*-bromoacetophenone. The limit for detection of α-haloacetophenones was experimentally estimated (GC and GC-IR) to be < 10^{-3} M to 10^{-4} M and a lower limit $k_{fY} > 10^9$ s^{-1} could be placed on the cleavage rate of α-bromo and α-chloroacetophenone ketyls. An estimated value, < 1×10^6 s^{-1}, has been reported for the bromide fragmentation from the ketyl of α-bromoacetophenone.[24] This result, obtained from a study of the products following the quenching of the photoexcited state of the carbonyl, does not appear to be in agreement with our electrochemically based determination.

Since the α-bromo and α-chloroacetophenone ketyls cleave at a rate > 10^9 s^{-1}, the following question is raised: is the ET to α-bromo- and α-chloroacetophenones dissociative, i.e. are the ET and the bond breaking concerted processes? Simple aliphatic and unsubstituted benzylic halides are now believed to undergo dissociative ET reactions.[25] The radical anions of nitro and cyanosubstituted benzyl halides, however, have been detected by pulse radiolysis[26] and fast cyclic voltammetry.[3,27] Although the EPR spectra of $CF_3X^{-\cdot}$ radical anions (X = Cl, Br, I) were observed in a solid matrix at 77K,[28] ET to CF_3X (X = Br, I) in a polar solvent (DMF) was recently proposed to be dissociative.[25e] The *p*-nitrophenacyl bromide ketyl (k_f = 4 x 10^4 s^{-1})[29] cleaves at about the same rate as that of the *p*-nitrobenzyl bromide radical anion (k_f = 1.7 x 10^5 s^{-1})[26a] in H_2O. From the comparison of the reported radical anion cleavage rate constants of the ring halogenated acetophenones and nitrobenzyl halides in H_2O[10,26] and in AN[3], it is evident that these radical anions cleave in AN about 30-1000 times faster than in H_2O. It can therefore be argued that the cleavage rate of *p*-nitrophenacyl bromide radical anion in AN ranges from 10^6 to 10^7 s^{-1}, and that the cleavage of the unsubstituted phenacyl bromide radical anion must be > 10^6 s^{-1} in AN. Since the ET to unsubstituted benzyl bromide is dissociative[25] and the α-bromoacetophenone ketyl cleaves at k > 10^9 s^{-1} (this work), the ET to α-bromoacetophenone is also likely to be dissociative. In a recent study of the photoreduction of α-bromoacetophenone by 10-methyl-9-acridan ($AcrH_2$) in acetonitrile, however, α-bromoacetophenone ketyl was proposed to be a discrete intermediate.[30] The photoreduction of α-bromoacetophenone with

[9,9'-$^2H_2$]-10-methylacridan ($AcrD_2$) in dry AN gave 100% monodeuteriated acetophenone ($PhCOCH_2D$). The product was, however, undeuteriated when 1 equivalent of H_2O was added to AN. It was suggested that the proton transfer within the radical ion pair (eq 17a) is faster than the ketyl cleavage (eq 17b). Although a sequence of multiple bimolecular reactions with rate constants faster than 10^9 M^{-1} s^{-1} between radical ion pairs in a solvent cage (ET-H^+-ET) might be possible, alternative explanations should be investigated.



(17)

The cleavage of α-substituents examined decreases in the order Br or Cl > F ≈ OCOPh > $OCOCH_3$ > OPh. The fast cleavage of the halide ions supports the suggestion[1f] that the halohydrin is more likely formed by a hydride transfer mechanism instead of by an ET-fast hydrogen atom transfer process during the enzymatic NADH reduction of α-haloacetophenones.

The intramolecular competitive reduction system also allows the determination of the cleavage rate constants of a new ring substituent, k_{fX}, from the measured k_{fY} using eq 16. The results for the determination of the *o*-Br, *p*-I and *m*-I acetophenone ketyl cleavage rate constants are included in Table V-2. Table V-3 summarizes our measured and also previously reported cleavage rate constants of substituted acetophenone ketyls. In agreement with previous observations,[3-4,10,26] the cleavage of the ring halogen decreases in the order I > Br > Cl and *o*-X > *p*-X > *m*-X.

Table V-3. The Cleavage Rate Constants of the Substituted Acetophenone Ketyls

$XC_6H_4COCH_3$ **Ia-h**	k_{fX} (s^{-1}) [a]	Reference	$PhCOCH_2Y$ **IVa-f**	k_{fY} (s^{-1}) [a]	Reference
Ia, X = *o*-Br	4×10^9	this work [b]	**IVa**, Y = Br	$> 10^9$	this work [b]
Ib, X = *p*-Br	3×10^7	3-4	**IVb**, Y = Cl	$> 10^9$	this work [b]
Ic, X = *m*-Br	8×10^3	3	**IVc**, Y = F	5×10^9	this work [b]
Id, X = *o*-Cl	3×10^5	3	**IVd**, Y = OCOPh	4×10^9	this work [b]
Ie, X = *m*-Cl	15	3	**IVe**, Y = OPh	10×10^6	this work [b]
If, X = *p*-Cl	3×10^3	3	**IVf**, Y = $OCOCH_3$	1×10^9	this work [b]
Ig, X = *p*-I	10×10^9	this work [b]			
Ih, X = *m*-I	1×10^8	this work [b]			

[a] RT, AN. [b] Average of the results reported in Table V-2.

3. New Chemical Probes for the ET Reactions of Enones

Enones are important synthetic intermediates and capable of undergoing a variety of chemical transformations.[31] Recently, the possible involvement of ET processes in the reactions of enones has been studied.[32] Our aim is to design a new chemical probe using radical anion fragmentation reactions as a clock for ET reactions. Ideally, the new probe should have the structural features that will allow the variation of fragmentation rates and the systematic studies of steric and electronic effects on the reaction mechanisms. Enones derived from the halogenated acetophenones, $XC_6H_4COCH{=}CR^1R^2$ (**V**), have the above necessary structural features. Bromochalcones, $XC_6H_4COCH{=}CHC_6H_5$, (**Va**, X = *p*-Br, R^1 = H, R^2 = Ph; **Vb**, X = *o*-Br, R^1 = H, R^2 = Ph) were chosen primarily because of their ease of preparation. The reaction of **Va-b** with DMBI was carried out in AN at 61 ^oC. The results are shown in Table V-4.

In the absence of AIBN only a very small amount (0.5%) of the debrominated product (chalcone, **VI**) was observed. In the presence of 4% AIBN the major product is chalcone (11%). About 1% of the 1,4-addition product, *p*-$BrC_6H_4COCH_2CH_2Ph$ (**VIIa**), was also detected by GC-IR (reactions 38-39, Table V-4). The initiated reduction of **Vb** also gave chalcone (19%), but no 1,4-addition product was detected (reaction 42, Table V-4).

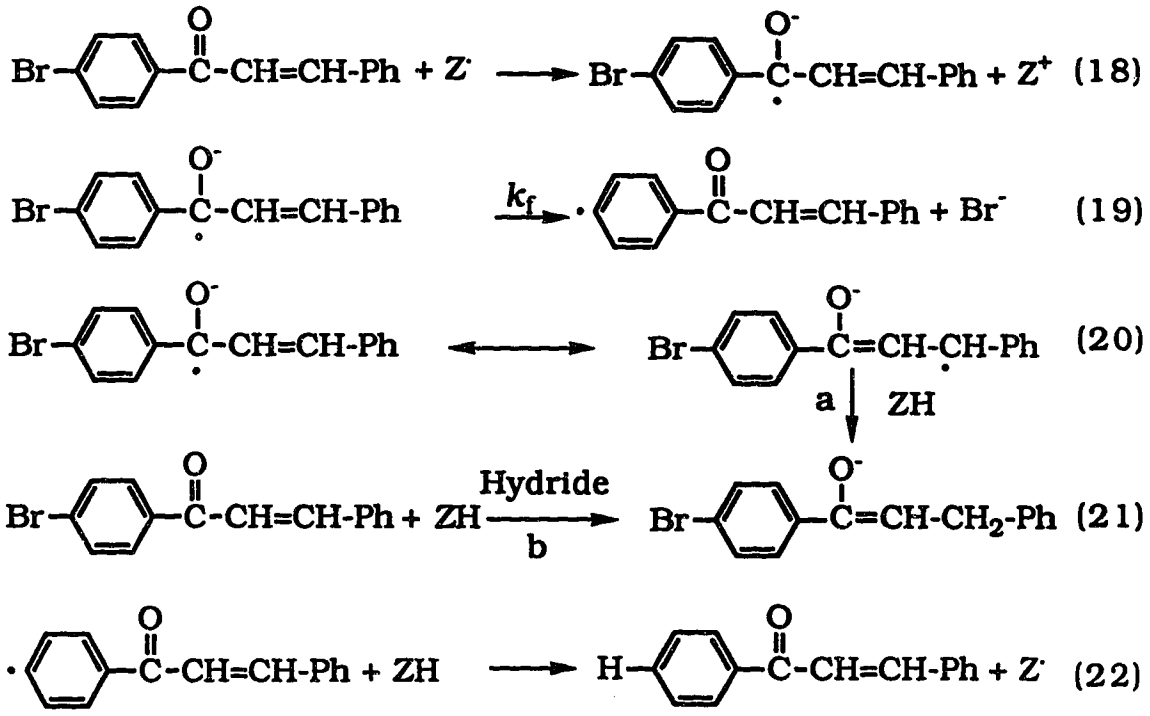
The AIBN initiated reduction of the bromochalcones to chalcone clearly proceeds via a free radical chain sequence. The 1,4-addition product (**VIIa**) observed in the DMBI reduction of **Va** in the absence of

Table V-4. The Reduction of the Bromochalcones (Va-b) by DMBI in AN

Rt. No.	Va-b	Reaction conditions [a]	Product (%)		
			Chalcone (VI)	$XC_6H_4COCH_2CH_2Ph$	Va-b
38	Va	61 °C, 64 h	0.5 ± 0.2	0.8 ± 0.2	100.1 ± 10.5
39		61 °C, 64 h, 4% AIBN	11.2 ± 3.5	1.0 [b]	86.1 ± 10
40		RT, 25 h, 111% $AlCl_3$	-	85.2 ± 2.0	10.8 ± 1.9
41		RT, 25 h, 111% $AlCl_3$, 10% DNB	-	87.6 ± 9.2	10.2 ± 5.7
42	Vb	61 °C, 58 h, 7% AIBN	19.0 ± 1.1	-	72.1 ± 5.8

[a] [DMBI] = [Va-b] = 0.05 M. [b] Estimated from the GC-IR measurement.

AIBN is formed by the direct hydride transfer sequence (eq 21b, Scheme V-4) instead of by the ET chain mechanism (eq 18, 20, 21a, Scheme V-4). If it was formed by hydrogen abstraction of the ketyl in the ET chain sequence, the yield would increase in the presence of AIBN.



ZH = DMBI

Scheme V-4. The Possible Mechanisms for the Reduction of *p*-Bromochalcone by DMBI

Although the bromochalcones are better electron acceptors than the bromoacetophenones, **Ia-c** (compare the reduction potential, E^{o}_{red}: chalcone, -1.41 V, SCE, DMF;[33] *m*-bromoacetophenone, -1.82 V, SCE, DMF[4]), they are less reactive towards DMBI than the bromoacetophenones. The cleavage rate constant of the bromide ion from *p*-bromoacetophenone ($k_{fX} = 3.2 \times 10^{7}$ s^{-1})[4] and *p*-bromobenzophenone ($k_{fX} = 4 \times 10^{4}$ s^{-1}, AN)[3] radical anions clearly indicates the effect of charge delocalization on the cleavage rate. Since the charge in the *p*-bromochalcone ketyl is more delocalized than the charge in the *p*-bromobenzophenone ketyl, the cleavage rate of *p*-bromochalcone ketyl is expected to be much slower. This prediction is supported by cyclic voltammetric experiments. *p*-Bromochalcone shows quasi-reversible redox peaks at a scan rate > 20 V/s. On the other hand, *m*-bromoacetophenone shows reversible redox peaks at a scan rate > 5000 V/s.[3] This result suggests that the slow ketyl cleavage of the bromochalcones is responsible for the short chain reduction of **Va-b**.

It has been reported that the reduction of enones such as chalcone by DMBI in the presence of $AlCl_3$ cleanly yielded a 1,4-reduction product.[34] From deuterium label studies two mechanisms, direct hydride transfer and ET-hydrogen atom transfer, were suggested. In an attempt to differentiate between these two mechanisms, we also studied the DMBI reduction of *p*-bromochalcone in the presence of $AlCl_3$. The reduction in the presence of $AlCl_3$ went smoothly at room temperature to give the 1,4-addition product, **VIIa**. No debrominated product was observed, and the reduction was not inhibited by DNB (reactions 40-41, Table V-4). These results suggest that a free radical

chain mechanism is not involved. The direct hydride transfer is therefore suggested for the $AlCl_3$ promoted DMBI reduction of enones.

The results of the DMBI reduction of bromochalcones indicate that due to the slow ketyl cleavage of the bromochalcones these enones are not suitable ketone fragmentation probes. The enones derived from the pivalaldehyde and haloacetophenones ($XC_6H_4COCH=CHBu^t$) are potentially much better probes since these enone radical anions would be expected to cleave much faster due to the reduced charge delocalization. Work is in progress in this laboratory on the chemistry of these new ET probes.

Conclusions

In this chapter the ET reductions of a series of haloacetophenones and their derivatives by DMBI have been studied. The intramolecular competitive reduction of α- and ring- substituted acetophenones was used to measure the cleavage rate constants of α-substituents and new ring substituents of substituted acetophenone radical anions. It was found that various α-substituted acetophenone ($PhCOCH_2Y$, Y = Br, Cl, F, OCOPh, $OCOCH_3$, OPh) radical anions undergo very fast cleavage. The study of these competitive reductions has made available a large number of ET probes with a wide range of electron affinity and ketyl cleavage rate constants.

Besides the apparent application to reactions with various nucleophilic reagents, these ketone fragmentation probes are useful in the study of the lifetime of radical anion intermediates formed in the

photoinduced ET reactions since the radical anion cleavage provides an internal clock to monitor other competing processes. Therefore, just like the radical cyclization and radical rearrangement clocks,[35] the radical anion fragmentation clocks described in this chapter should have broad applications.

Experimental

1. Materials

The purification or preparation of **DMBI**, **DNB**, **AIBN**, **di-*tert*-butylbenzene**, **bibenzyl**, **acetonitrile**, **α-haloacetophenones (IVa-c)**, **acetophenone**, and **DBPO** has been described in Chapter 2 of the thesis. The preparation of **α-(phenoxy)acetophenone (IVe)**, **α-(benzoyloxy)acetophenone (IVd)**, and **α-(acetoxy)acetophenone (IVf)** was described in Chapter 4.

Ring brominated or chlorinated acetophenones (*o*,*m*,*p*) (Ia-f) (Aldrich), ***p*-bromobenzophenone (IIa**, Fluka), and **chalcone (VI**, Aldrich) were used as supplied. The purity, checked by GC, was at least 97%.

Mesityl phenyl ketone and ***p*-bromophenyl mesityl ketone (IIb)** (provided by C. Yang) were prepared according to the literature procedure.[36]

α,*p*-Dibromoacetophenone (IIIa) (Aldrich, Fluka) was recrystallized from ethanol, mp 108-9.5 °C (lit.[37] 108-9 °C).

***p*-Bromo-α-chloroacetophenone (IIIb)** was prepared by the chlorination of *p*-bromoacetophenone with sulfuryl chloride.[38] Sulfuryl chloride (4.5 mL, 0.056 mol) was added slowly to the ketone (10 g, 0.05 mol). The mixture was stirred at room temperature for an hour. Excess sulfuryl chloride was removed using a rotatory evaporator. The residue was recrystallized several times from ethanol to give white

crystals, mp 118-119.5 °C (lit.[39] 119-20 °C); ^{1}H NMR δ 4.58 (s, 2 H), 7.65 (m, 2H), 7.85 (d, 2 H).

***p*-Bromo-α-fluoroacetophenone (IIIc)** was prepared by the fluorination of α,*p*-dibromoacetophenone with potassium fluoride.[40] It was extremely important to dry the commercial potassium fluoride to obtain the fluoroketone. Thus KF (9 g, 0.15 mol) was dried over a very hot flame for 45 min and cooled in a desiccator over P_2O_5. It was then added to a mixture of α,*p*-dibromoacetophenone (15 g, 0.053 mol) in dry AN (60 mL) containing a catalytic amount (~ 0.1 g) of 18-crown-6. The mixture was subsequently refluxed for 69 h. Acetonitrile was then removed and the residue was extracted with ether. After the removal of ether, the red residue was taken up by ethanol (98%, 50 mL) and filtered. The filtrate upon evaporation gave 4 g of the crude product. The product was recrystallized from a water-ethanol mixture and dried over P_2O_5 in vacuo to give pale yellow crystals, mp 70-72 °C; ^{1}H NMR δ 5.5 (d, 2 H, J = 46 Hz), 7.75 (m, 4 H). Anal. Calcd for C_8H_8BrFO: C, 44.27; H, 2.79. Found: C, 44.18; H, 2.68.

All the bromomethyl aryl ketones ($ArCOCH_2Br$) used in this study were prepared from the corresponding methyl aryl ketones ($ArCOCH_3$) and copper bromide according to the literature procedure for the bromination of ketones.[41] They were purified either by distillation or by recrystallization, or they were used directly in the synthesis of **III**. All the esters ($ArCOCH_2OCOPh$) were prepared according to the literature procedure from $ArCOCH_2Br$, $PhCO_2H$, and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[42] The phenyl ethers were

synthesized from $ArCOCH_2Br$, PhOH, and DBU (for a typical procedure see the preparation of **IIIe**).

α-Benzoyloxy-*p*-bromoacetophenone (IIId), mp 119-120 °C (lit.[43] mp 120-121 °C); ^1H NMR δ 5.5 (s, 2 H), 7.5 (m, 2 H), 7.65 (m, 3 H), 7.85 (d, 2 H), 8.15 (d, 2 H). Anal. Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47. Found: C, 56.21; H, 3.48.

***p*-Bromo-α-phenoxyacetophenone (IIIe)** was synthesized according to the following procedure. A mixture of α,*p*-dibromoacetophenone (14 g, 0.05 mol), phenol (4.7 g, 0.05 mol), and DBU (6.8 g, 0.05 mol) in benzene (70 mL) was stirred at room temperature for 24 h. The salt ($DBUH^+Br^-$) was filtered and washed with benzene. The filtrate was washed with H_2O, 5% NaOH, 2N HCl and H_2O, and dried over magnesium sulfate. A dark red solid was obtained after the evaporation of the solvent. The crude product was recrystallized from ethanol to give pale yellow crystals, mp 91.5-92.5 °C (lit.[44] 92-3 °C); ^1H NMR δ 5.37 (s, 2 H), 7.1 (m, 3 H), 7.45 (m, 2 H), 7.9 (d, 2 H), 8.05 (d, 2 H). Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.76; H, 3.81. Found: C, 57.38; H, 3.82.

α-Benzoyloxy-*o*-bromoacetophenone (IIIi), mp 65-6 °C; ^1H NMR δ 5.5 (s, 2 H), 7.25-7.65 (m, 7 H), 8.05-8.15 (m, 2 H). Anal. Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47. Found: C, 56.32; H, 3.33.

***o*-Bromo-α-fluoroacetophenone (IIIh)** was synthesized using the same procedure as *p*-bromo-α-fluoroacetophenone, bp 100-120 °C (4 mmHg); ^1H NMR δ 5.4 (d, 2 H, J = 48 Hz), 7.3-7.7 (m, 4 H). GC, GC-IR, GC-MS, and ^1H NMR showed that it contained 11% of *o*-bromoacetophenone. This amount was corrected for the yield of *o*-bromo-

acetophenone formed in the reduction with DMBI. The DMBI reduction of **IIIh** did not produce any significant amount (< 0.8%) of acetophenone, the product of the reduction of *o*-chloroacetophenone or α-phenoxyacetophenone by DMBI.

***o*-Chloro-α-phenoxyacetophenone (IIIg)**, bp 185-188 °C (3 mmHg); ^{1}H NMR δ 5.2 (s, 2 H), 6.9-7.1 (m, 3 H), 7.25-7.7 (m, 6 H); MS (*m/e*): 248.04 and 246.04. GC-IR, ^{1}H NMR, and GC showed it contained 4.3% of *o*-chloroacetophenone. This amount was corrected for the yield of *o*-chloroacetophenone formed in the reduction with DMBI. The DMBI reduction of **IIIg** did not produce any significant amount (< 0.5%) of acetophenone, the product of the reduction of *o*-bromoacetophenone or α-phenoxyacetophenone by DMBI.

***p*-Iodoacetophenone (Ig)** was synthesized from *p*-aminoacetophenone according to the literature procedure.[45] A solution of $NaNO_2$ (13.3 g, 0.19 mol) in H_2O (28 mL) was added slowly to a cooled (5 °C) solution of *p*-aminoacetophenone (25 g, 0.19 mol) in water (186 mL) containing concentrated sulfuric acid (30 mL). The resulting dark solution was poured into a cooled solution of KI (40 g, 0.24 mol) in water (30 mL). The mixture was stirred at room temperature for 2 h and then heated on a steam bath until no N_2 evolved. The mixture was then cooled to room temperature, filtered, and washed with water, aqueous sodium bisulfite, aqueous sodium hydroxide, and water. The solid was dissolved in ether and washed with 5% NaOH and H_2O. After evaporation and recrystallization from hexane, yellow crystals were obtained, mp 85.5-86.5 °C (lit.[46] 85 °C); ^{1}H NMR δ 2.58 (s, 3 H), 7.7-7.8 (d, 2 H), 7.8-7.9 (d, 2 H). ***m*-Iodoacetophenone (Ih)** was prepared

similarly, bp 142-150 °C (6.5 mmHg) [lit.[47] 128.5 °C (8 mmHg)]; ^{1}H NMR δ 2.6 (s, 3 H), 7.2-7.4 (m, 1 H), 7.8-8.0 (m, 2 H), 8.3-8.4 (m, 1 H). Anal. Calcd for C_8H_7IO: C, 39.05; H, 2.87. Found: C, 38.72; H, 2.89.

α-Benzoyloxy-*m*-iodoacetophenone (IIIk), mp 102-103 °C; ^{1}H NMR δ 5.5 (s, 2 H), 7.2-7.6 (m, 4 H), 7.8-8.3 (m, 5 H). Anal. Calcd for $C_{15}H_{11}IO_3$: C, 49.21; H, 3.03. Found: C, 49.23; H, 2.95.

α-Benzoyloxy-*p*-iodoacetophenone (IIIj), mp 127.5-128.5 °C (lit.[48] 128 °C); ^{1}H NMR δ 5.55 (s, 2 H), 7.4-7.7 (m, 5 H), 7.8-8.0 (d, 2 H), 8.1-8.2 (d, 2 H). α-Bromo-*p*-iodoacetophenone, mp 113-114 °C (lit.[48] 113.5 °C); ^{1}H NMR δ 4.4 (s, 2 H), 7.7 (d, 2 H), 7.9 (d, 2 H).

α-Acetoxy-*p*-bromoacetophenone (IIIf) was prepared according to the literature procedure, mp 84.5-85.5 °C (lit.[42] 85-86 °C); ^{1}H NMR δ 2.25 (s, 3 H), 5.3 (s, 2 H), 7.4-7.8 (m, 4 H).

***p*-Bromochalcone (Va)** was prepared according to the literature procedure,[49] mp 102-3 °C (lit.[49] 100-2 °C); ^{1}H NMR δ 7.4-8.0 (m, 11 H). ***o*-Bromochalcone (Vb)** was prepared similarly, bp 215-6 °C (2.5 mmHg) [lit.[50] 183-5 °C(2 mmHg)]; ^{1}H NMR δ 7.0-7.8 (m, 11 H). Anal. Calcd for $C_{15}H_{11}BrO$: C, 62.74; H, 3.86. Found: C, 62.84; H, 3.77.

3-Phenyl-*p*-bromopropiophenone (VIIa) was prepared by the reduction of *p*-bromochalcone with DMBI in the presence of $AlCl_3$ on a preparative scale.[34] $AlCl_3$ (0.16 g, 1.2 mmol) was added to a cooled solution of **Va** (0.278 g, 1 mmol) and DMBI (0.275 g, 1.2 mmol) in AN (8 mL) in a pyrex tube. The solution was degassed and sealed. After heating for 8 h at 61 °C, the tube was opened. The reaction mixture was hydrolyzed with 0.1M HCl (3 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined CH_2Cl_2 solution was washed with water, dried

with magnesium sulfate, and evaporated. The resulting crude product was purified by column chromatography on silica gel (eluent: toluene/petroleum ether = 1/1) and by recrystallization from ligroin, mp 98-9 °C (lit.[51] 101 °C); ^{1}H NMR δ 3.12 (t, 2 H, J = 7.5 Hz), 3.35 (t, 2 H, J = 7.5 Hz), 7.3 (m, 5 H), 7.65 (d, 2 H), 7.9 (d, 2 H).

Tris(2,2'-bipyridyl)ruthenium diperchlorate was synthesized according to the literature method.[52]

2. Methods and Procedures

Physical constant measurements, microanalyses, spectral measurements, and GC analyses were carried out using the same instruments described in Chapter 2 of this thesis.

Several columns were routinely employed for GC analysis:

(A) A stainless steel column (10 ft x 1/8 in.) packed with 5% OV-101 on Chromosorb WAW DMCS 100/200 mesh; (B) a stainless steel column (10 ft x 1/8 in.) packed with 5% SE-30 on Chromosorb WAW DMCS 80/100 mesh; (C) a stainless steel column (10 ft x 1/8 in.) packed with 5% FFAP on Chromosorb WAW DMCS 60/80 mesh; and (D) a DB-5 megabore column (30 m, J&W Scientific Inc.). The internal standard was either *p*-di-*tert*-butylbenzene or bibenzyl.

Column D was used on a Varian 3700 Gas Chromatograph with a TCD detector connected to a Varian CDS 401 data station. Other columns were used on an HP 5840A gas chromatogrph interfaced to an HP 5840A intergrator. The GC analyses of the reaction mixture of α-fluoroacetophenone derivatives (**IIIc** and **IIIh**) were carried out on

column D or C. The reaction mixture of all other ketones was analyzed by GC using column A or B. The separation of products was achieved by using either one of the two columns. For all reactions, GC-IR was run on an Ultral-2 column (25 m) and GC-MS on a DB-5 column (see Chapter 2 for the detailed description of these columns).

The yields of reaction products in the competitive reduction of disubstituted acetophenones were measured from GC-IR experiments for yields lower than 2%. For yields higher than 2% the same results were obtained from GC-IR and GC measurements. The quantitative calculation of yields from GC-IR experiments used the relative intensities of the IR spectra and the relative areas obtained from the FID detector connected to the GC-IR. A standard solution was run to obtain the response factor. The same equation for the calculation of yields in the GC analysis (see Chapter 2) was employed. A known concentration of a standard solution was analysed by GC-IR to obtain its detection limit for the compound (see the tables).

General Procedure for the Reduction. A mixture of the substrate (0.05 M), the reagent (DMBI), 0.025-0.05 M), the internal standard (0.02 M), and the additive (AIBN, DNB, DBPO, or $Ru(bpy)_3^{2+}$, 1.7-14%) was placed in a pyrex ampule. The ampule was degassed three times, sealed, and thermostated at the desired temperature for the time specified in Table V-1 to V-5. The ampule was opened and analyzed by GC. For each new reaction the products were further identified by the comparison of their GC-IR and GC-MS spectra with those of authentic samples.

The reduction of **IIIa-b** and the reduction initiated by DBPO were modified to avoid possible reactions during degassing. A solution (1 mL) of the substate, internal standard, and the additives, and a solution (1 mL) of DMBI were each put in the separate arms of an H-form ampule. After being degassed, sealed, and thermostated at room temperature, the solutions in the two arms were mixed and kept at room temperature in the dark for the specified time.

The photostimulated reduction was carried out in a thick straight pyrex tube. After the solution was degassed, the tube was put inside a test tube filled with a filter solution of $K_2Cr_2O_7$-$NaNO_2$-NaOH[21] which was capable of absorbing 450-500 nm light. The distance between the test wall and the reaction tube (light path) was 1 cm. The test tube was put in a water bath and was irradiated with 2 x 200 W incandescent light bulbs. The water bath was kept at 20 °C.

The competitive rate of the DMBI reduction of *p*-iodo and *p*-bromoacetophenone (**Ig** and **Ib**, k_{Ig}/k_{Ib}), and the competitive rate of the DMBI reduction of *p*-bromobenzophenone (**IIa**) and *p*-bromophenyl mesityl ketone (**IIb**, k_{IIa}/k_{IIb}) were determined by the disappearance of the starting substrates. The general procedure discussed in Chapter 2 was followed for the measurement of k_{Ig}/k_{Ib} and k_{IIa}/k_{IIb}.

The Procedure for the Reduction of *o*-Bromoacetophenone by Sodium Dithionite. The literature procedure for the reduction of carbonyl compounds by sodium dithionite was followed.[39] The crude product (93%) was found to contain neither $PhCOCH_3$ nor $PhCHOHCH_3$ by GC-IR and GC-MS. The GC-IR detection limit for $PhCOCH_3$ or $PhCHOHCH_3$ (> 0.05% of the starting ketone) was

obtained by analyzing a known concentration of a standard solution of these two compounds. Only the corresponding alcohol (*o*-$BrC_6H_4CHOHCH_3$) (MS: *m/e*, 206, 204, 188, 186, 156, 158, 79, 78, 77, and 46; IR: cm^{-1} 3652, 3076, 1569, 1438, 1312, 1131, 1016, and 931) was detected by GC-MS and GC-IR.

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1988.6	The Graduate Research Travel Award by FGSR
1986-1990	Teaching assistantship by the Department of Chemistry, University of Alberta
1988	The 1987 Margaret Thompson Memorial Book Prize by the Department of Chemistry

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