

PROJECT ADMINISTRATION DATA SHEET

☒ X

ORIGINAL



REVISION NO. _____

Project No. G 33-679DATE: 6/19/81Project Director: E. C. AshbySchool/Lab ChemistrySponsor: National Science FoundationWashington, D.C. 20550Type Agreement: Grant No. CHE-8101124Award Period: From 6/1/81 To 11/30/82 (Performance) 2/28/83 (Reports)Sponsor Amount: \$85,800

Contracted through:

Cost Sharing: \$ 6,194 (G33-363)GTRI/~~XXX~~Title: Organometallic Reaction Mechanisms: the Importance of Single Electron Transfer Pathways

ADMINISTRATIVE DATA

OCA CONTACT Don Hasty1) Sponsor Technical Contact: Kenneth G. Hancock(202) 357-79562) Sponsor Admin./Contractual Contact: Ms. Paulette L. Greene(202) 357-9630Reports: See Deliverable Schedule Security Classification: N/ADefense Priority Rating: N/A

RESTRICTIONS

See Attached NSF Supplemental Information Sheet for Additional Requirements.Travel: Foreign travel must have prior approval - Contact OCA in each case. Domestic travel requires sponsor approval where total will exceed greater of \$500 or 125% of approved proposal budget category.Equipment: Title vests with N/A - None ProposedCOMMENTS: NSF intends to continue for a total of 36 months at the same level each year, pending availability of funds and the scientific progress of the project.

COPIES TO:

Administrative Coordinator
Research Property Management
Accounting Office
Procurement/EES Supply ServicesResearch Security Services
~~Reports Coordinator (OCA)~~
Legal Services (OCA)
Library, Technical ReportsEES Research Public Relations (
Project File (OCA)
Other: _____

SPONSORED PROJECT TERMINATION/CLOSEOUT SHEET

Date 8/9/85

Project No. G-33-679

School/~~XXX~~ CHEM

Includes Subproject No.(s) _____

Project Director(s) E.C. Ashby

GTRC /~~GTR~~

Sponsor National Science Foundation

Title Organometallic Reaction Mechanisms: The Importance of Single Electron Transfer Pathways

Effective Completion Date: 11/30/84 (Performance) 2/28/85 (Reports)

Grant/Contract Closeout Actions Remaining:

- ☐ None
- ☐ Final Invoice or Final Fiscal Report
- ☐ Closing Documents
- ☒ ~~Final Report~~ Patent Questionnaire
- ☐ Govt. Property Inventory & Related Certificate
- ☐ Classified Material Certificate
- ☐ Other _____

Continues Project No. _____ Continued by Project No. _____

COPIES TO:

Project Director
Research Administrative Network
Research Property Management
Accounting
Procurement/GTRI Supply Services
Research Security Services
Reports Coordinator (OCA)
Legal Services

Library
GTRC
Research Communications (2)
Project File
Other A. Jones; M. Heyser

SR519 2 - N-B-T

OCA

G-33-679

GEORGIA TECH RESEARCH INSTITUTE
ADMINISTRATION BUILDING
GEORGIA INSTITUTE OF TECHNOLOGY
ATLANTA, GEORGIA 30332

Telex: 542507 GTRIOCAATL
Fax: (404) 894-3120

Phone: (404) 894- 4815

10 March 1983

Refer to: LHB/G407-83-22

National Science Foundation
1800 G Street, N.W.
Washington, D.C 20550

Attention: Dr. Luis A. Echegoyen
Program Office for Chemical Dynamics

Subject: Grant No. CHE-8101124; Request for Incremental
Funding for Continuing Grant entitled, "Single
Electron Transfer, A Major Reaction Pathway"

Gentlemen:

In accordance with NSF Grant Policies, the GTRI is pleased to submit the Annual Progress Report and Request for Continued Support on the subject research project.

We believe that the enclosed material will provide you with all necessary information. However, if additional information is required, please contact Dr. E. C. Ashby at 404/894-4040 concerning the technical program. Contractual matters should be referred to the undersigned at 404/894-4815.

We appreciate the opportunity of submitting this request and look forward to the possibility of continuing our work with you on this project.

Cordially,

Linda H. Bowman
Linda H. Bowman
GEORGIA TECH RESEARCH INSTITUTE

LHB/sm

Addressee: In duplicate
Enclosure: Progress Report - in duplicate
Proposal Budget - in duplicate

Georgia Institute of Technology

A UNIT OF THE UNIVERSITY SYSTEM OF GEORGIA

ATLANTA, GEORGIA 30332

CHEMISTRY

February 25, 1983

Dr. Luis A. Echegoyen
Program Office for Chemical Dynamics
National Science Foundation
Washington, DC 20550

Dear Luis:

Attached is a copy of our NSF Annual Report (June 1, 1982 - May 31, 1983). I'm sorry I am a little late, but arranging the XI International Conference on Organometallic Chemistry has taken more time than I thought.

Research this past year has been very exciting and productive. I hope that this attitude is reflected in the report.

Sincerely,



E. C. Ashby
Regents' Professor of Chemistry

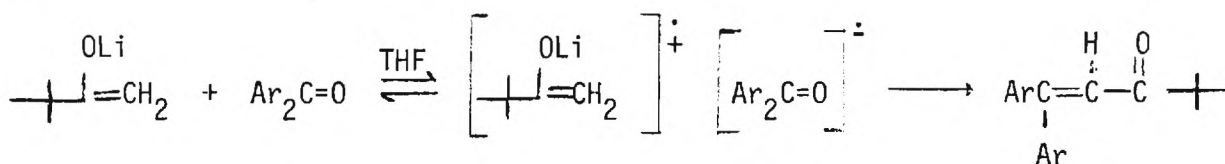
af
Attachment

SINGLE ELECTRON TRANSFER. A MAJOR REACTION PATHWAY.

The past year has been very fruitful in that four major studies were begun and completed. The studies involve the following reactions: Aldol Condensation, Cannizzaro Reaction, Claisen Condensation, and the Corey-House Reaction. In each case we were able to demonstrate that single electron transfer (SET) is involved in the cases that were studied.

(1) "Evidence for a Single Electron Transfer Mechanism in Aldol Condensation Reactions," J. Amer. Chem. Soc., 104, 6788 (1982).

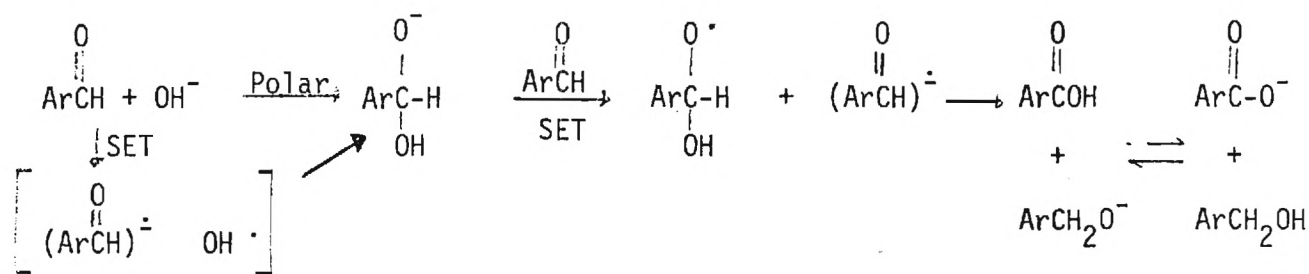
We have been able to demonstrate that the reaction of enolates (prepared separately) react with aromatic ketones by a SET process. The mechanism is given below.



The SET nature of the mechanism was established by demonstrating that the rate of disappearance of the paramagnetic intermediate as observed by esr was equal to the rate of formation of the product. The complete details are given in the attached publication.

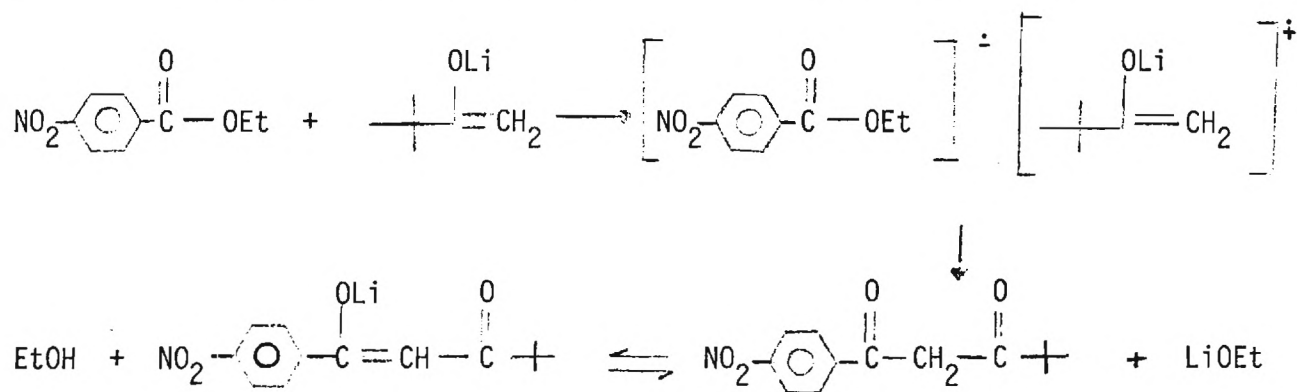
(2) "Evidence Supporting a Single Electron Transfer Pathway in the Cannizzaro Reaction," Tetrahedron Letters, 851 (1983).

We have been able to demonstrate that the reaction of NaOH with substituted benzaaldehydes in THF and THF/HMPA (9:1 ratio) proceeds via an electron transfer pathway. Resolved epr spectra of the paramagnetic intermediates were shown to be identical to the intermediates formed from the same aldehydes and sodium in THF. The mechanism is shown below.



(3) "Evidence for Single Electron Transfer in Claisen Condensation," Tetrahedron Letters, (1983).

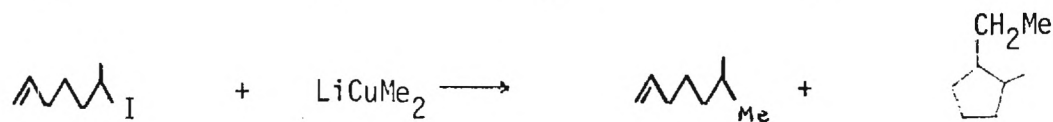
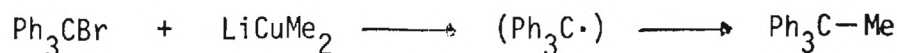
We have been able to show that enolates react with ethyl-p-nitrobenzoate in THF by electron transfer. The proposed mechanism is given below.



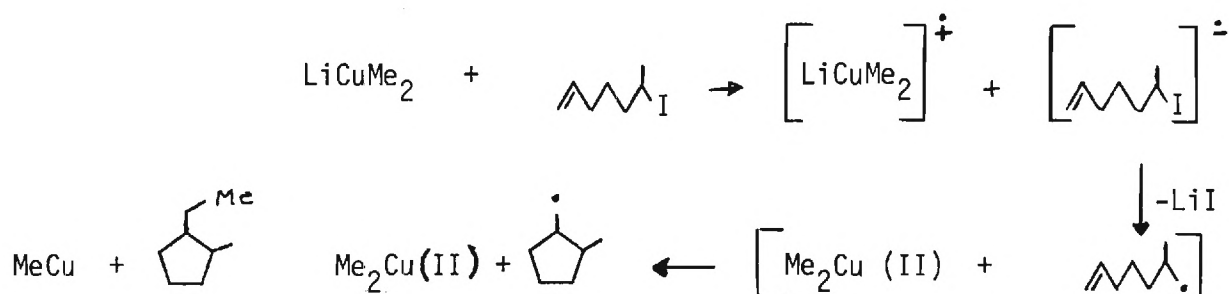
The mechanism is supported by the fact that the product is formed at the same rate that the paramagnetic intermediate disappears.

(4) "Evidence for a Single Electron Transfer Mechanism in Reactions of Lithium Diorganocuprates with Organic Halides." Tetrahedron Letters, 5251. (1982).

It has been demonstrated by means of spectroscopic studies involving trityl bromide and cyclizable alkyl halides that LiCuMe_2 can react with organic halides by a single electron transfer pathway.



The observation of trityl radical (3-5%) and cyclized hydrocarbon in the two reactions above indicate the intermediate radical formation. The proposed mechanism of the reaction is shown below.



Budget

We anticipate no remaining funds for the present research period.

Current Support and Pending Proposals

We have no proposals pending and, as has been the case for some years, our entire work is sponsored by NSF and PRF. Our current PRF grant (# 14102-AC4-C) is dated from 9/1/82 to 8/31/85 and is for \$45,000 for the three year period. The title of the PRF proposal is, "Single Electron Transfer in Organic Reactions." The PRF effort, unlike the NSF effort, is entirely in the area of organometallic reactions; whereas, the NSF effort involves non-organometallic reactions.

EVIDENCE SUPPORTING A SINGLE ELECTRON TRANSFER PATHWAY IN THE REDUCTION OF
AROMATIC KETONES BY METAL ALKOXIDES. LITHIUM ISOPROPOXIDE, AN EXCELLENT
REDUCING AGENT FOR AROMATIC KETONES.

E.C. Ashby*, Anil B. Goel and John N. Argyropoulos
School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332 USA

SUMMARY: Reactions of various metal alkoxides with aromatic ketones have been shown to produce radical intermediates. Lithium isopropoxide has been found to be an excellent reducing agent for aromatic ketones and reduces benzophenone at a faster rate than does aluminum isopropoxide.

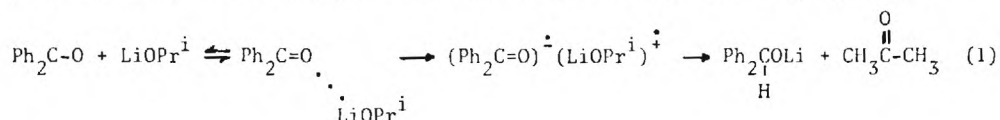
The degree of polar and radical character exhibited in reactions of typical nucleophilic reagents with organic substrates has been the subject of recent interest.^{1,2} The mechanisms of these reactions have been proposed mainly on the basis of stereochemical observations, kinetics, product formation studies and radical anion trapping. Recently, we proposed the possible involvement of a single electron transfer (SET) pathway in reactions of lithium amides and lithium (and potassium) alkoxides with organic substrates such as alkyl halides and polynuclear hydrocarbons.³ The basis of the proposed SET mechanism was the appearance of radical intermediates (observed by EPR spectroscopy) and product formation studies using cyclizable probes. More recently, we have shown that the reduction of $\text{Ph}_2\text{C}=\text{O}$ with LiNPr^i_2 proceeds via a radical intermediate.⁴ Russell⁵ has generated fluorenone ketyl by reacting alkoxides with fluorenone however, he did not observe reduction product. On the other hand, Screttas⁶ has observed reduction product in the case of benzophenone and alkoxide, but did not directly observe the ketyl precursor. In view of these results, we decided to study the mechanism of reduction of ketones with metal alkoxides, not only lithium and potassium alkoxides, but also $\text{Al}(\text{OPr}^i)_3$ involving the classic Meerwein-Ponndorf-Verley reduction⁷ which has been well recognized to proceed via a polar mechanism.

We have observed the formation of radical intermediates in the reactions of aromatic ketones [benzophenone and mesitylphenylketone (MPK)] not only with metal alkoxides such as LiOPr^i , LiOBu^n , LiOBu^t , $\text{LiOCH}_2^t\text{Bu}$ and $\text{KO}-t\text{-Bu}$, but also with $\text{Al}(\text{OPr}^i)_3$, (eq. 1). The reduction product (Ph_2CHOM), of course, is only formed in the reaction of alkoxide reagents containing α -hydrogen atoms.

When a solution of freshly prepared lithium alkoxide, LiOR(I) (where $\text{R} = i\text{-Pr}$, $n\text{-Bu}$, $t\text{-Bu}$ and $\text{CH}_2\text{-}t\text{-Bu}$) and $\text{KO}-t\text{-Bu(II)}$ was mixed with $\text{Ph}_2\text{C}=\text{O}$ in THF under nitrogen at room temperature, a blue colored solution developed slowly in every case. These solutions were found to be paramagnetic (showed complex EPR spectra),

indicating the formation of an intermediate radical species. Interestingly, the solutions of different alkoxide reagents provided a different EPR spectrum (see Figures 1a, 1b and 2), thus suggesting that the radical intermediate is not the free ketyl. This point was further confirmed by comparing the spectra of the various reactions with those of the free ketyls prepared independently. The amounts of the radical intermediates were found to increase slowly with time and the rate of increase was found to be dependent on the nature of the alkoxy group of the reagent. The rate of radical formation followed the trend: $i\text{-Pr} > \text{CH}_2\text{-}t\text{-Bu} > n\text{-Bu} > t\text{-Bu}$ in the lithium alkoxide series. Thus while LiOPr^i generated a reasonable concentration of radical intermediate ($\sim 5\%$) within ten hours only a trace amount of radical was detected in reactions involving LiOBu^t . Interestingly, KOBU^t was observed to react with $\text{Ph}_2\text{C=O}$ to produce a radical intermediate at a much faster rate than LiOBu^t . No reduction product was formed in those cases where no α -hydrogen is present in the alkoxides although electron transfer is observed.

The importance of the steric requirement of the reagent (alkoxy groups) as well as the substrate (aromatic ketone) was also observed in the product formation studies. In the reactions of a sterically bulky ketone (MPK) with sterically bulky alkoxide reagents (such as $\text{LiOCH}_2\text{OBu}^t$) either none or only a trace amount of reduction product was formed even after warming to 50°C . This observation suggests that the hydrogen transfer step of the reaction is affected significantly by the steric demands of the intermediates. The total observations reported above can be best explained by the mechanism represented by equation 1.



In the reaction of LiOPr^i and $\text{Ph}_2\text{C=O}$ in 2:1 molar ratio in THF at room temperature, the highest concentration of radical intermediate was 14% after one day. While the radical concentration was increasing with time, the product of the reaction continuously formed and after one day about 45% reduction product was isolated. After the radical concentration reached a maximum, the EPR signal slowly decreased and after 3 days disappeared completely. At this time, no starting benzophenone was detectable in the reaction mixture and the product was formed in essentially quantitative yield.

In view of the above results involving lithium alkoxides, we decided to carry out the classic Meerwein-Ponndorf-Verley reduction involving $\text{Al(OPr}^i)_3$ as the reducing agent. When freshly distilled $\text{Al(OPr}^i)_3$ (trimer or tetramer) and

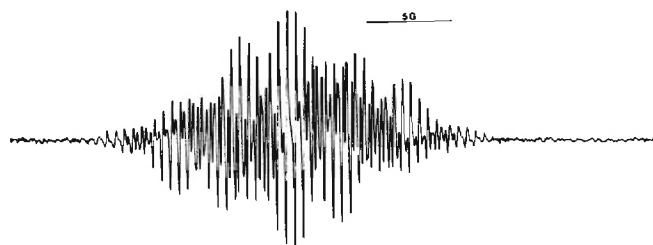


Figure 1A: EPR spectrum of the intermediate formed in the reaction of benzophenone with lithium isopropoxide in THF at room temperature

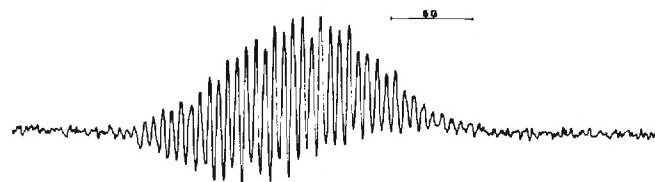


Figure 1B: EPR spectrum of the intermediate formed in the reaction of benzophenone with lithium neopentoxide in THF at room temperature.

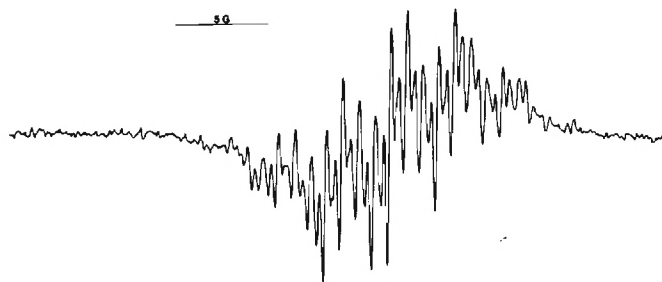


Figure 2: EPR spectrum of the intermediate formed in the reaction of benzophenone with potassium t-butoxide in THF at room temperature.

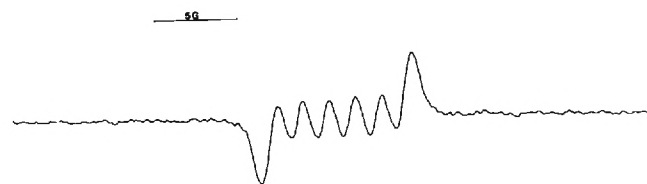


Figure 3: EPR spectrum of the intermediate formed in the reaction of benzophenone with $\text{Al}(\text{OPr}^i)_3$ in THF at room temperature.

$\text{Ph}_2\text{C}=\text{O}$ or MPK were mixed in THF, an EPR signal (Fig. 3) was observed immediately. The intensity of the signals indicated the concentration of radicals to be $\sim 1\%$. The EPR signal resembled that of the expected radical cation. These signals decayed slowly and completely disappeared within two hours. When the reaction mixture was heated to 50°C for 7 hours, a new signal developed (trace amount) which resembled that of the radical anion (e.g., in the case of MPK, a quartet with 4-5 G spacing, appeared which can be explained as the splitting due to ortho- and para protons of the phenyl ring). In the case of $\text{Ph}_2\text{C}=\text{O}$, reduction product was obtained whereas MPK gave only a trace amount of reduction product after 7 days. It is quite possible that if the radical mechanism is operative here, the rates of the first step (electron transfer) and the second step (coupling of radicals) are comparable so that little or no radical concentration can develop. We did not observe the formation of the trityl radical in the reaction of $\text{Al}(\text{OPr}^i)_3$ with Ph_3CBr whereas LiOPr^i did react to form the trityl radical $(\text{Ph}_3\text{C}\cdot)^3$. Similarly, no radical could be detected in the reaction of $\text{Al}(\text{OPr}^i)_3$ with polynuclear hydrocarbons.

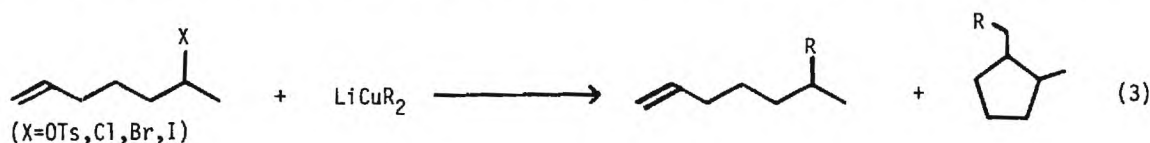
REFERENCES:

1. E.C. Ashby and J.S. Bowers, *J. Amer. Chem. Soc.*, **103**, 2242, (1981); E.C. Ashby, A.B. Goel and R.N. DePriest, *J. Amer. Chem. Soc.*, **102**, 7779, (1980) and references therein. N. Kornblum, *Angew Chem.*, (Internat. Ed.) **14**, 734, (1975).
2. F.G. Bordwell and A.H. Clemens, *J. Org. Chem.*, **46**, 1037, (1981); and references therein.
3. E.C. Ashby, A.B. Goel and R.N. DePriest, *J. Org. Chem.*, **46**, 2429, (1981).
4. E.C. Ashby, A.B. Goel and R.N. DePriest, *Tetrahedron Lett.*, (submitted for publication).
5. G.A. Russell and E.G. Janzen, *J. Amer. Chem. Soc.*, **84**, 4163, (1962).
6. C.G. Screttas and C.T. Cazianis, *Tetrahedron*, **34**, 933, (1978).
7. A.L. Wilds, in "Organic Reaction", Vol. II, edited by R. Adams, W.S. Bachmann, I.E. Feiser, J.R. Johnson and H.R. Snyder, John Wiley & Sons, New York, NY (1957), p. 178.

(Received in USA 10 December 1981)

development of a yellow-orange color, which increased in intensity with time and then slowly decreased. The reaction solutions were found to be EPR active and exhibited a spectrum in each case consistent with that of the trityl radical.⁹ The solutions of the trityl halides under the conditions of these reactions were shown not to be EPR active. The concentration of the radical increased rapidly with time and reached a maximum within a few minutes (estimated intensity $\approx 3\text{--}5\%$). Beyond the maximum, the radical concentration decreased slowly with the concurrent formation of the product, 1,1,1-triphenylethane, which was formed in 90% yield.

Since it has been demonstrated that $\text{LiCu}(\text{CH}_3)_2$ is capable of reacting with organic halides by an electron transfer process, as a further test it was decided to examine the reactions of lithium diorganocuprates with cyclizable alkyl halide probes, such as the 6-halo-1-heptenes. Therefore, if indeed an intermediate species having radical character is formed during the coupling reaction, it should be possible to observe cyclized coupled product (eq.3). Hence, the reactions of several lithium diorganocuprates with 6-halo-1-heptenes were examined.



Earlier we had demonstrated that higher order cuprates, such as Li_2CuMe_3 , exhibit enhanced reactivity toward secondary alkyl halides relative to the reactivity of LiCuMe_2 ; ¹⁰ therefore, the reactions of the 6-halo-1-heptenes with Li_2CuMe_3 were also investigated.

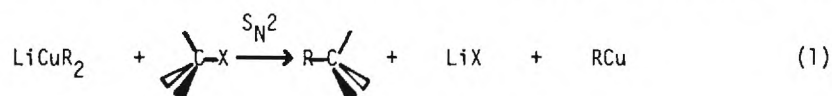
The results of reactions of several lithium diorganocuprates with several 6-halo-1-heptenes are given in Table 1. Unfortunately, LiCuEt_2 , LiCuPh_2 and $\text{LiCu}(\text{n-C}_6\text{H}_{13})_2$ gave only elimination products upon reaction with 6-bromo-1-heptene or 6-iodo-1-heptene (exps. 1-4). However, substantial amounts of coupled products were formed in the reactions utilizing the methylcuprates. When $\text{X}=\text{OTs}$ (exps. 5 and 9) and when $\text{X}=\text{Br}$ (exps. 7 and 11) the only coupled product is the straight-chain 6-methyl-1-heptene for reactions with either LiCuMe_2 , or Li_2CuMe_3 . However, when $\text{X}=\text{I}$ (exps 8 and 12), the major product of reaction with either LiCuMe_2 or Li_2CuMe_3 is the cyclic coupled product, 1-ethyl-2-methylcyclopentane, in $\approx 65\%$ yield. Also, small amounts of 1,2-dimethylcyclopentane were formed in reactions of the iodo and bromo compounds, which may be an indication of an intermediate radical species which cyclizes and then abstracts a H-atom from the solvent. It should be noted that 6-chloro-1-heptene was found to be completely unreactive toward LiCuMe_2 or Li_2CuMe_3 . The most striking feature of these results is that the secondary iodo compound reacts with LiCuMe_2 and Li_2CuMe_3 by a pathway that is fundamentally different than that of the other secondary halides. Our interpretation of these data is that the iodo compound reacts by a pathway involving predominantly electron transfer, whereas the bromide reacts by a pathway that is predominantly, but not exclusively

EVIDENCE FOR A SINGLE ELECTRON TRANSFER MECHANISM
 IN REACTIONS OF LITHIUM DIORGANOCUPRATES WITH ORGANIC HALIDES

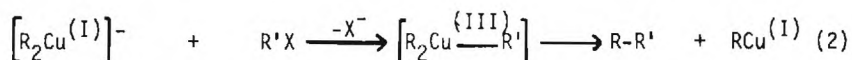
E.C. Ashby*, R.N. DePriest, A. Tuncay and Sushil Srivastava
 School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332 USA

Abstract: It has been demonstrated by means of spectroscopic studies involving cyclizable alkyl halides that lithium dimethylcuprate can react with organic halides by a single electron transfer pathway.

The reaction of lithium diorganocuprates (LiCuR_2) with alkyl halides is of major synthetic importance.¹ Since LiCuR_2 compounds can be readily prepared from organolithium reagents and copper (I) halides, coupling reactions with alkyl halides have been studied in considerable detail. Perhaps the most significant mechanistic studies have involved stereochemically defined systems. The fact that lithium dialkenylcuprates are known to couple with various alkyl halides with retention of configuration has been used as an argument against the intervention of free radical species as intermediates.² Also, it has been demonstrated that LiCuPh_2 reacts with optically active 2-bromobutane and 2-butyl tosylate with predominant inversion of configuration.^{3,4} Thus, it has been proposed that the coupling reaction of a dialkylcuprate with an alkyl halide proceeds by an $\text{S}_{\text{N}}2$ pathway, as described in equation (1).¹ However, an alternative pathway has been suggested which involves an oxidative addition of the alkyl halide to the cuprate, followed by a reductive elimination of the hydrocarbon product,



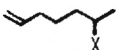

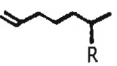

as described in equation (2).⁵⁻⁷ The oxidative addition mechanism includes a copper (III)



organometallic species, which has also been described as a copper(II)-radical complex.⁸

In order to determine if cuprate reagents are capable of reacting by an electron transfer pathway, we decided to examine the reaction of LiCuMe_2 with trityl halides by EPR. Since the trityl radical is relatively stable, it should be possible to observe it as an intermediate if indeed an electron transfer pathway is operative. Lithium dimethylcuprate was allowed to react with trityl chloride and bromide in ether at 0° to -5°C, and the reactions were followed by EPR spectroscopy at the same temperature. These reactions proceeded rapidly with the

Table 1. Reactions of Lithium Diorganocuprates with 6-Halo-1-heptenes in THF^a.

Exp.	X in 	Cuprate	Temp.	PRODUCTS (%)			
				Dienes ^b	 (trans/cis)	 R	 (trans/cis)
1	Br	LiCuEt ₂	-20 ⁰	96	trace	0.0	0.0
2	Br	LiCuPh ₂	8 ⁰	98	trace	0.0	0.0
3	Br	LiCu(n-Hex) ₂	-30 ⁰	95	0.0	0.0	0.0
4	I	LiCu(n-Hex) ₂	-30 ⁰	95	0.0	0.0	0.0
5	OTs	LiCuMe ₂	8 ⁰	22	0.0	24 ^c	0.0
6	Cl	LiCuMe ₂	8 ⁰	trace	0.0	0.0 ^c	0.0
7	Br	LiCuMe ₂	8 ⁰	1.1	4.5(3.1)	68	0.0
8	I	LiCuMe ₂	8 ⁰	1.8	6.0(3.2)	18	65(0.23)
9	OTs	Li ₂ CuMe ₃	8 ⁰	5.0	0.0	20 ^c	0.0
10	Cl	Li ₂ CuMe ₃	8 ⁰	trace	0.0	0.0 ^c	0.0
11	Br	Li ₂ CuMe ₃	8 ⁰	2.6	9.6(7.7)	64	0.0
12	I	Li ₂ CuMe ₃	8 ⁰	1.5	10.7(1.1)	14	62(0.22)

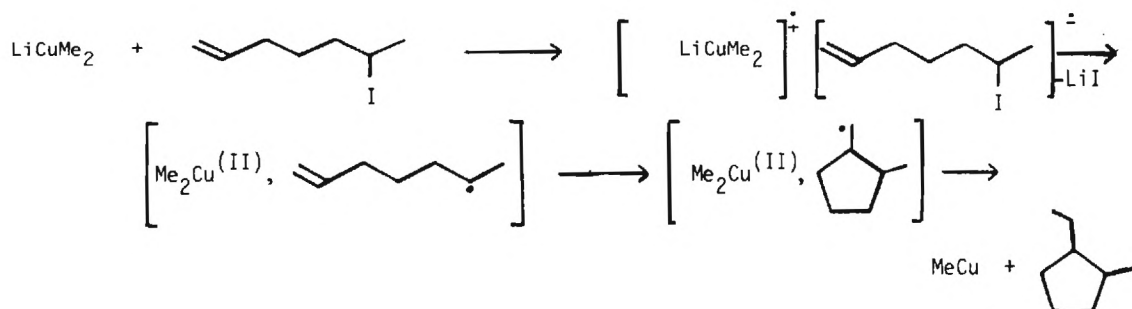
a Cuprate reagents were prepared by the addition of the required amount of organolithium compound to CuBr suspended in THF, according to known procedures.² Product yields were determined by g.l.c. and all reactions were allowed to proceed for a period of 72 hours.

b Mixture of 1,5- and 1,6-heptadienes.

c Recovered substrate accounts for material balance.

S_N2 . A mechanistic proposal to account for these results is given in Scheme I.

SCHEME I



In conclusion, these studies clearly show that LiCuMe_2 and Li_2CuMe_3 do indeed react with organic iodides by an electron transfer pathway. Since we have shown recently that an electron transfer process can proceed with inversion of configuration,¹¹ we are actively pursuing stereochemical studies of the coupling reactions of organic halides with organocuprate reagents.¹²

REFERENCES:

1. G.H. Posner, "Org. React.", **22**, 253 (1975).
2. (a) G.M. Whitesides and C.P. Casey, Jr., *J. Am. Chem. Soc.*, **88**, 4541 (1966).
(b) K. Mori and S. Tamada, *Tetrahedron*, **35**, 1279 (1979).
3. C.R. Johnson and G.A. Dutra, *J. Am. Chem. Soc.*, **95**, 7783 (1973).
4. G.M. Whitesides, W.F. Fischer, Jr., J. San Filippo, Jr., R.W. Bashe and H.O. House, *J. Am. Chem. Soc.*, **91**, 4871 (1969).
5. J. Kochi, A. Bemis and C.J. Jenkins, *J. Am. Chem. Soc.*, **90**, 4616 (1968).
6. H.O. House and M.J. Umen, *J. Am. Chem. Soc.*, **94**, 5495 (1972).
7. E.J. Corey and I. Kuwajima, *J. Am. Chem. Soc.*, **92**, 395 (1970).
8. J.K. Kochi and F. Rust, *J. Am. Chem. Soc.*, **83**, 2017 (1961).
9. F.C. Adam and S.I. Wiesman, *J. Am. Chem. Soc.*, **80**, 2057 (1958).
10. E.C. Ashby and J.J. Lin, *J. Org. Chem.*, **42**, 2805 (1977).
11. E.C. Ashby and R.N. DePriest, *J. Am. Chem. Soc.*, in press (1982).
12. We are indebted to the National Science Foundation, Grant No. (CHE 78-00757) for support of this work.

(Received in USA 27 August 1982)

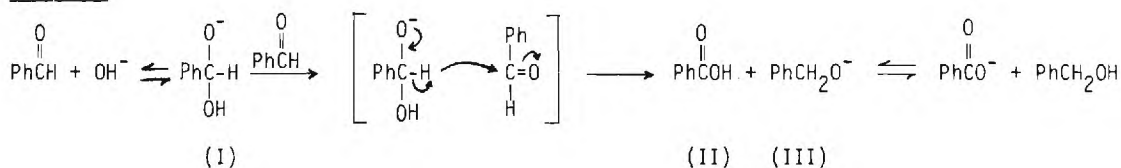
EVIDENCE SUPPORTING A SINGLE ELECTRON TRANSFER PATHWAY IN THE CANNIZZARO REACTION

E. C. Ashby*, David T. Coleman III and M. Pilar Gamasa
 School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332 USA

Abstract: Radical species are observed by EPR spectroscopy in the Cannizzaro reaction involving various substituted benzaldehydes with NaOH in THF/HMPA (9:1). The radical species have been identified as the aldehyde radical anions corresponding to the particular aldehyde studied.

The Cannizzaro reaction has been considered one of the most fundamental reactions in organic chemistry.¹ It involves the reaction of an aldehyde, devoid of α -hydrogens, with a high concentration of a strong base (e.g. NaOH) to form an equimolar mixture of the corresponding primary alcohol and the salt of the corresponding carboxylic acid. Thus substituted aromatic aldehydes are prime candidates for this oxidation-reduction reaction. A variety of mechanisms for this reaction have been proposed,² however the mechanism presently accepted invokes a hydride transfer (Scheme I). Radical chain mechanisms have been suggested, but have

Scheme I



been discounted on the basis that neither radical initiators nor inhibitors have a decisive effect on the rate of reaction.³ Recently, however, Chung has shown⁴ a possible involvement of radical intermediates in the Cannizzaro reaction involving benzaldehyde- α -d in alkaline aqueous dioxane and dioxane alone. His conclusion was based on the fact that a substantial amount of benzyl alcohol- α -d₁ was produced in the reaction in addition to the normal product, benzyl alcohol- α -d₂. The monodeuterated product suggests the formation of the benzaldehyde radical anion followed by hydrogen atom abstraction from the solvent.

We have studied the Cannizzaro reaction by EPR spectroscopy and have obtained evidence for the existence of paramagnetic species in solution. Benzaldehyde and a number of substituted benzaldehydes were allowed to react with NaOH in THF/HMPA (9:1 ratio) and the resulting mixture studied by EPR spectroscopy. The results of these studies are tabulated in the Table. In three cases (p-chloro-, p-trifluoromethyl-, and p-cyanobenzaldehyde) the EPR spectra of the

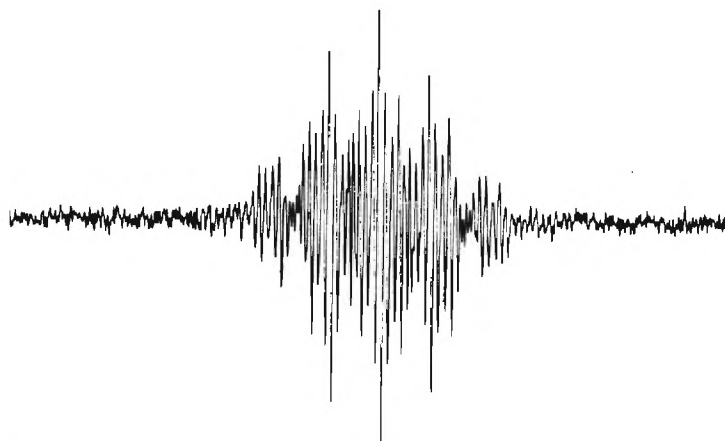


Figure 1: EPR spectrum of the intermediate formed in the reaction of NaOH with p-trifluoromethylbenzaldehyde in THF/HMPA (9:1) at room temperature.

Table. Reactions of aromatic aldehydes with NaOH in THF/HMPA (9:1 ratio) at 25°C.

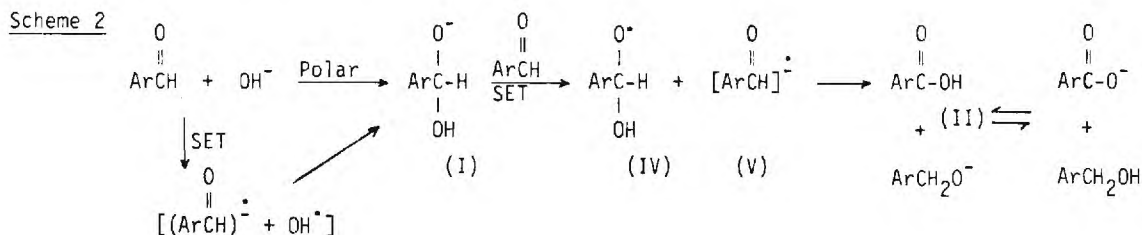
Benzaldehyde	EPR Signal	% Yield Products		
		Alcohol ^{c,d}	Acid ^{c,e}	Total
p-Cl	resolved ^a	95.0	91.6	93.3
p-CF ₃	resolved ^a	93.0	86.6	89.9
p-CN	resolved ^a	82.1	88.4	85.3
p-H	unresolved	58.5	52.4	84.5 ^f
p-NO ₂	resolved ^b			
o-CH ₃	unresolved			
2,4,6-(CH ₃) ₃	no signal			
(CH ₃) ₃ C ^O CH	no signal			

All reactions were carried out in the dark, under N₂ with [aldehyde] = 0.36M in HMPA/THF solution (1:9 ratio) and the ratio of aldehyde:NaOH was 2:1.5. Reaction times were 24 hrs for all reactions except benzaldehyde, which was allowed to react for 36 hrs. All aldehydes were distilled from CaH₂, except p-nitrobenzaldehyde which was doubly sublimed, THF was distilled from Na/benzophenone and HMPA was distilled from sodium. ^aSpectrum was compared to a spectrum of the reaction product obtained from the reaction of sodium with the aldehyde in the same solvent system. ^bSpectrum is similar to the free radical anion of p-nitrobenzaldehyde. ^cAlcohol and acid yields based on 1/2 of the total moles of starting aldehyde. ^dYield determined by NMR. ^eYield determined by base titration and the acid identified by neutralization equivalent and comparison of the IR spectrum with that of an authentic sample. ^fTotal yield based on starting aldehyde includes 13.7% of recovered aldehyde and 15.3% of benzyl benzoate. Aldehyde and ester yields were determined by NMR.

reacting solutions were well resolved and the spectra obtained are identical to the spectra produced from the reaction of sodium metal with each respective aldehyde in the same solvent system.⁵ This suggests that the radical obtained in the reaction of NaOH with each of the aldehydes is the free radical anion of the respective aldehyde. The EPR spectrum of the intermediates formed on reaction of p-trifluoromethylbenzaldehyde with NaOH in THF/HMPA is given in the figure. In the case of p-nitrobenzaldehyde, the spectrum was interpreted and found to be similar to the radical anion of p-nitrobenzaldehyde. Of the seven aromatic aldehydes studied, only 2,4,6-trimethylbenzaldehyde failed to produce a radical signal by EPR spectroscopy. α - α - α -Trimethylacetaldehyde was also allowed to react under the same conditions, but no EPR signal was observed presumably due to the high reduction potential of aliphatic aldehydes compared to aromatic aldehydes.

Due to the insolubility of NaOH in the solvent system used, the reactions carried out in the EPR tubes did not go to completion. Attempts to increase the solubility of NaOH to a satisfactory level by use of a variety of different aprotic solvents (DMF, DME, HMPA, DMSO) and of KOH in the presence of 18-crown-6 were not successful. Therefore, stirred larger scale reactions of p-chloro, p-trifluoromethyl-, p-cyanobenzaldehyde, and benzaldehyde were carried out using the same concentrations and conditions as those used in the EPR tube reactions. The isolated yields are given in the Table. The Cannizzaro reaction proceeds well to give reasonable yields of the acid and alcohol products with the exception of benzaldehyde which is complicated by the formation of the ester from the alcohol and acid.

Resolved EPR signals of the substituted benzaldehyde radical anions and high yields of Cannizzaro products under similar conditions suggest that the Cannizzaro reaction in these cases is proceeding by a single electron transfer mechanism. Unfortunately a more direct correlation relating the appearance and disappearance of the radicals with the appearance of the products was not possible due to the insolubility of NaOH in the solvents used. However all of the data presented here indicate that aromatic aldehydes react with NaOH under the conditions described here to form Cannizzaro product by a SET pathway. The suggested mechanism is presented in Scheme 2.



It can be seen that intermediate (I) can be formed by either of two pathways. We feel confident that the SET pathway is possible since we have independent evidence that OH^- is a good single electron donor. In this connection we have allowed NaOH in THF to react with both trityl bromide and p-dinitrobenzene. Significant amounts of trityl radical and p-dinitrobenzene radical anion were observed by EPR spectroscopy. The reaction of (I) with

the aromatic aldehyde by a SET pathway is also reasonable since we have already shown that alkoxides can transfer an electron to alkyl halides,⁶ ketones⁷ and polynuclear hydrocarbons.⁸ It is presumably at this stage that we are observing the aldehyde radical anion. The aldehyde radical anion (V) can then abstract a hydrogen atom from IV to produce the Cannizzaro products.

In conclusion, these studies indicate the the Cannizzaro reaction involving aromatic aldehydes is proceeding at least to some extent by a single electron transfer pathway. Further studies are underway.

REFERENCES:

1. T.A. Geissman, Org. React., **II**, 94 (1944).
2. C.G. Swain, Arnet L. Powell, William A. Sheppard and Charles R. Morgan, J. Am. Chem. Soc., **101**, 3576 (1979), and references cited therein.
3. a) K.H. Geib, Z. Phys. Chem. Abt. A, **169**, 41 (1934). b) E. R. Alexander, J. Am. Chem. Soc., **69**, 289 (1947).
4. Sung-Kee Chung, J. C. S. Chem. Comm., 480 (1982).
5. Coupling constants were not determined due to the complexity of the spectra. Furthermore, in the literature there is data available only for the p-cyanobenzaldehyde radical anion.
a) P. H. Rieger and G. K. Frankel, J. Chem. Phys., **37**, 2811 (1962). b) J. Dubois and G. Dodin, J. Amer. Chem. Soc., **94**, 7520 (1972).
6. Unpublished results.
7. E. C. Ashby, Anil B. Goel, and John N. Argyropoulos, Tetrahedron Lett., **23**, 2273 (1982).
8. E. C. Ashby, A. B. Goel, and R. N. DePriest, J. Org. Chem., **46**, 2429 (1981).

(Received in USA 8 November 1982)

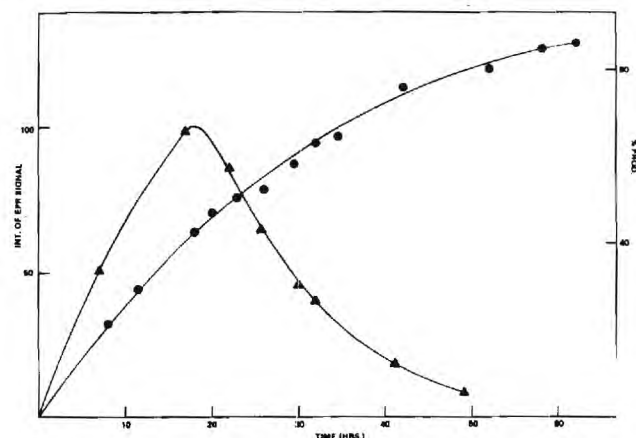


Figure 1. Reaction of benzophenone (0.08 M) with the lithium enolate of pinacolone in THF: (▲) intensity of EPR signal (mm) vs. time, where 1 mm = 0.001% radical; (●) condensation product (%) vs. time (h).

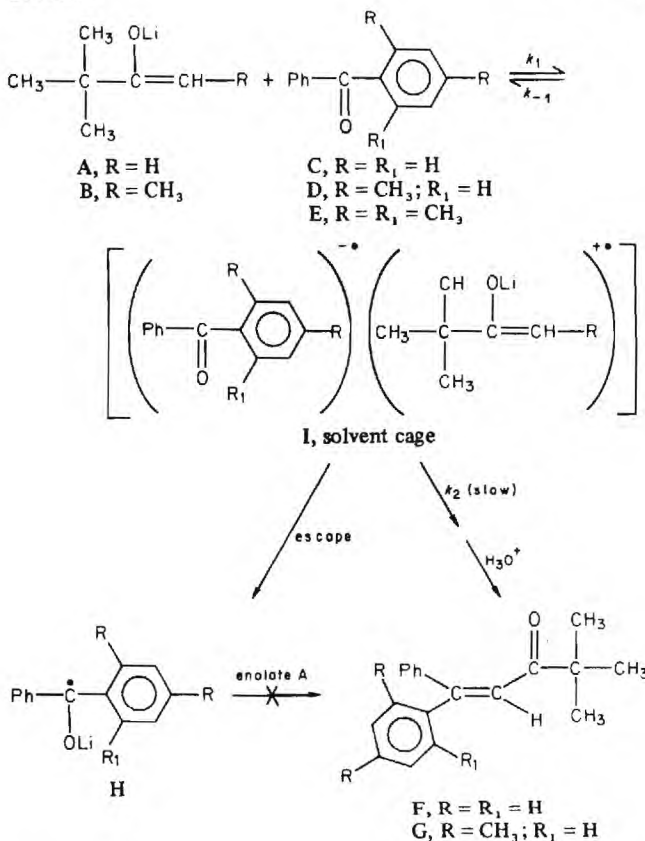
that the intensity of the EPR signal reaches a maximum at 18 h, beyond which decay proceeds in a first-order fashion over a period of 2 days. The concentration of benzophenone decreases rapidly during the time that the signal for the paramagnetic species is increasing, and after 18 h the rate of formation of product is the same as the rate of decay of the paramagnetic species.

On the basis of the results of these two reactions, a mechanistic scheme (Scheme I) involving a radical anion-radical cation pair as the intermediate is proposed. When enolate B was allowed to react with benzophenone, coupling of the radical anion-radical cation did not occur to give condensation product (presumably due to steric reasons), and in time, the radical anion escaped from the solvent cage leading to a large buildup of the free, stable radical anion of benzophenone. However, when the less sterically hindered enolate A was allowed to react with benzophenone, condensation product did form. The first-order decay of the radical intermediate in this reaction suggests that it is the radical anion-radical cation pair (I) instead of the free ketyl (H). The first-order rate constant k_2 for the disappearance of the paramagnetic intermediate is $2.3 \times 10^{-5} \text{ sec}^{-1}$. As seen from Scheme I, the free ketyl (H) does not react with enolate A, since the lithium ketyl of benzophenone prepared independently did not react with pinacolone enolate to give product. Furthermore, when dicyclohexylphosphine was used in 10 mol % relative to benzophenone, no effect on the rate of formation of product was observed, thus providing further evidence that the free ketyl (H) is not involved in the product-forming step.¹¹ The overall reaction was second order with a rate constant of $4.5 \times 10^{-5} \text{ s}^{-1} \text{ M}^{-1}$ at 25.0 °C.

The possibility that a radical-chain mechanism may be operating in the reaction of benzophenone with enolate A was investigated by carrying out reactions under normal laboratory light, in the dark, and in the presence of 5 mol % *p*-dinitrobenzene. In all the cases the rate of formation of product was essentially the same. The effect of 10% HMPA or Me_2SO in THF on the reaction of enolate A with benzophenone was also studied. In these solvents the rates of formation of the radical intermediate and product are greater than in pure THF. This observation is consistent with an expected accelerated rate for the formation of the intermediate and product in solvents of higher dielectric constant.

Enolate A was also allowed to react with 2,4-dimethylbenzophenone in THF in the hope of increasing the amount of radical intermediate by slowing down k_2 (Scheme I). The condensation product (G) formed in 30% yield over a period of 9 days. The maximum amount of radical generated in this reaction was approximately 10 times greater than the amount of paramagnetic intermediate generated when benzophenone and enolate A were allowed to react. The reaction of enolate A with mesityl phenyl ketone gave an even larger amount of paramagnetic intermediate

Scheme I



(5% free ketyl); however, no product was formed in the reaction. A similar observation was made when mesityl phenyl ketone was allowed to react with enolate B. Such observations are consistent with the mechanism presented in Scheme I.

In conclusion, it has been demonstrated by ESR spectroscopy that typical enolate anions react with aromatic ketones by an electron-transfer process to produce a paramagnetic intermediate. A kinetic analysis shows that the paramagnetic intermediate formed in the reaction of enolate A with benzophenone disappears at the same rate that the condensation product forms.¹² A steric effect seems to be operating in the reaction of benzophenone and its substituted derivatives with the lithium enolates studied that governs not only the rate of formation of condensation product but also the amount of radical generated. Large amounts of free ketyl are observed when the pathway to condensation product is blocked by steric hindrance (k_2 step in Scheme I). When the product is observed, the amount of paramagnetic intermediate is much smaller though dependent on the rate at which product forms. We are now pursuing further characterization of the ESR active species that arise in these reactions as well as extending the work reported here to other carbonyl compounds and lithium enolates.

Registry No. A, 70367-67-8; B, 64869-29-0; C, 119-61-9; D, 1140-14-3; E, 954-16-5; F, 844-39-3; G, 83511-33-5; I, 83511-31-3; lithium benzophenone ketyl, 16592-10-2; lithium mesityl phenyl ketone ketyl, 59671-59-9; lithium 2,4-dimethylbenzophenone ketyl, 83511-32-4; dicyclohexylphosphine, 829-84-5; *p*-dinitrobenzene, 100-25-4; benzhydrol, 91-01-0.

(12) With the assumption that the reaction is at equilibrium after 18 h, the following analysis can be made:

$$\begin{aligned} d[\text{F}]/dt &= k_2[\text{I}] = k_2K[\text{A}][\text{C}] = k'[\text{A}][\text{C}] \\ -d[\text{I}]/dt &= k_2[\text{I}] + k_{-1}[\text{I}] - k_1[\text{A}][\text{C}] = k_2[\text{I}] \end{aligned}$$

$K = k_1/k_{-1} = 0.99$ was estimated by calculating the extent of electron transfer between benzophenone and various lithium enolates where radical intermediate but no condensation product was formed. Hence $k' = 4.5 \times 10^{-5} \text{ s}^{-1} \text{ M}^{-1} \approx 2.3 \times 10^{-5} \text{ s}^{-1} \text{ M}^{-1} = k_2K$.

(11) Dicyclohexylphosphine was shown to be an efficient trap for benzophenone ketyl, yielding benzhydrol quantitatively.

Evidence for a Single-Electron-Transfer Mechanism in Aldol Condensation Reactions

E. C. Ashby,* J. N. Argyropoulos, G. Richard Meyer, and A. B. Goel

*School of Chemistry, Georgia Institute of Technology
Atlanta, Georgia 30332*

Received April 22, 1982

The condensation of an aldehyde or ketone in the presence of a base (Aldol condensation) is an important synthetic reaction, the mechanism of which is considered to be polar in nature.^{1,2} Nevertheless, the ability of enolate anions to transfer a single electron to various organic substrates is well documented.³⁻⁶ Recently, we reported the involvement of a single-electron-transfer (SET) mechanism in reactions of various nucleophiles with aromatic ketones.⁷⁻⁹ We now report evidence consistent with the involvement of a SET mechanism in aldol condensation reactions involving enolate nucleophiles with aromatic ketones.

When the lithium enolates of 2,2-dimethyl-3-butanone (pinacolone, A) and 2,2-dimethyl-3-pentanone (B) were allowed to react with benzophenone (C), 2,4-dimethylbenzophenone (D), and mesityl phenyl ketone (E), EPR active species were generated in all cases. For example, when enolate B was allowed to react with benzophenone in a 1.5:1 mole ratio, respectively, in THF at 25 °C, a blue color appeared within a few hours. This colored solution gave rise to a well-resolved EPR spectrum, as well as a visible spectrum (λ_{max} 632 nm), both of which are similar to the EPR

and visible spectra recorded for an authentic sample of lithium benzophenone ketyl (prepared by the rxn of lithium metal with benzophenone in THF). The concentration of the free ketyl (H) reached a maximum after 1 week and was calculated to be approximately 10% relative to benzophenone.¹⁰ After this period of time when the reaction was quenched, benzophenone was recovered in nearly quantitative yield.

In contrast, the reaction of enolate A with benzophenone under exactly the same conditions gave a high yield (90%) of the condensation product, 4,4-dimethyl-1,1-diphenyl-1-penten-3-one (F) in 3 days. EPR analysis of the reaction mixture showed the existence of a paramagnetic species formed in small (~0.1%) concentration. The signal was too weak to resolve. Figure 1 shows

(1) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin; Menlo Park, CA 1972.

(2) Caine, D. S. In "Carbon-Carbon Bond Formation"; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. I.

(3) Russell, G. A.; Janzen, E. G.; Strom, E. T. *J. Am. Chem. Soc.* **1964**, *86*, 1807.

(4) Russell, G. A.; Mudryk, B.; Jawdoskiuk, M. *J. Am. Chem. Soc.* **1981**, *103*, 4610.

(5) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734.

(6) Bunnett, J. F.; Singh, P. *J. Org. Chem.* **1981**, *46*, 5022 and references cited therein.

(7) Ashby, E. C.; Goel, A. B.; DePriest, R. N. *Tetrahedron Lett.* **1981**, *22*, 4355.

(8) Ashby, E. C.; Goel, A. B.; Park, W. S. *Tetrahedron Lett.* **1981**, *22*, 4209.

(9) Ashby, E. C.; Goel, A. B.; Argyropoulos, J. N. *Tetrahedron Lett.* **1982**, *23*, 2273.

(10) The standard used was 2,2,5,5-tetramethylpyrrolidine-3-carboxamide 1-oxy in THF. The peak heights of the ketone radical and standard were compared.

Evidence for Inversion of Configuration in Reactions Involving Radical Processes

E. C. Ashby* and Robert DePriest

School of Chemistry, Georgia Institute of Technology
Atlanta, Georgia 30332

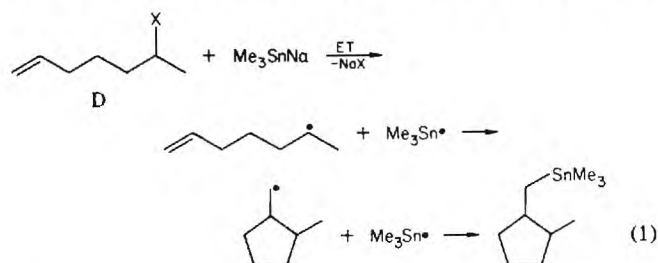
Received February 26, 1982

Revised Manuscript Received August 6, 1982

In recent years Kuivila and others have reported the occurrence of electron transfer in reactions of alkyl halides with R_3SnNa and R_3SnLi compounds to form tetraalkyltin compounds.¹⁻⁴ More recently, Kuivila has reported the use of trapping agents, such as dicyclohexylphosphine (DCPH), which convert radical intermediates to the corresponding hydrocarbons.⁵ Thus, by examination of the effects of added trapping agents on the above reaction, the extent of reactions by S_N2 , halogen-metal exchange (HME), or electron-transfer (ET) pathways for a variety of alkyl halides have been quantified. In general, alkyl chlorides and bromides were found to react by S_N2 , ET, and HME pathways to varying extents, depending on the structure of the alkyl group. In contrast to the work of Kuivila, San Filippo recently reported that the reaction of trimethyltin sodium with (-)-2-bromooctane proceeds with inversion of configuration.⁶ Kuivila, however, reported earlier that the racemate of the substrate studied by San Filippo, (\pm)-2-bromooctane, reacts with Me_3SnNa by a reaction pathway that involves predominant (72%) electron transfer. Thus, the lack of extensive racemization during the substitution reaction studied by San Filippo led him to state that "the additives which were employed as trapping agents must be introducing a substantial perturbation on the mechanism", and he further implied that mechanistic conclusions obtained by the use of such trapping agents cannot be applied to the same reaction when conducted without the use of traps. We believe that the earlier conclusions of Kuivila, that DCPH is an effective radical trap, are indeed correct. In an attempt to clarify this apparent dichotomy, we have carried out studies to indicate the radical nature of the reaction and also the stereochemistry of the reaction.

Previous studies involving a cyclizable alkyl halide free radical probe have employed 6-bromo-1-hexene with the result that only

straight-chain tetraalkyltin products were formed⁷ (Scheme I). Scheme I indicates that if k_3 is substantially greater than k_4 , no cyclized product should be found even if the reaction involves radical character along the reaction pathway. On the other hand, the rate of coupling (k_3) of A and B should decrease with an increase in the steric requirement of A. Such an effect would result in a better chance of observing the cyclized product C if the reaction is indeed preceeding by an ET process. In addition, the 2-octyl halide system studied by San Filippo would be more accurately mimicked by a secondary halide probe. With this in mind, the reaction of Me_3SnNa with several 6-halo-1-heptenes, D, was examined (eq 1, Table I). When X = OTs, the only



substitution product formed has the straight-chain structure, and furthermore, DCPH has no effect on the reaction, indicating that the reaction is proceeding predominantly by an S_N2 pathway with little or no ET involved. When X = Cl (experiments 3, 4), a substantial portion of the substitution product is cyclized, indicative of radical character along the reaction pathway. Also, it is clear that DCPH is an effective radical trap and is trapping the radical more rapidly than it is cyclizing. On the other hand, DCPH has no effect on the yield of straight-chain tetraalkyltin compound, although the yield of cyclic substitution product decreased. Thus, it seems likely that the straight-chain substitution products formed from D when X = Cl or OTs are the result of direct S_N2 displacement. However, it is also clear that some reaction has taken place by an ET pathway for X = Cl, as evidenced by the formation of cyclic substitution product. When X = Br (experiments 5, 6), the major product is the cyclized substitution product (71–72%). As in the previous case where X = Cl, DCPH proved to be an effective radical trap by reducing the amount of cyclized substitution product (72–14%) while increasing substantially the

(1) San Filippo, J., Jr.; Silberman, J.; Fagan, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 4834.

(2) Lyding, J. M. Ph.D. Dissertation, University of California, Berkeley, CA, 1977.

(3) Kitching, W.; Olszowy, H.; Waugh, J. J. *Org. Chem.* **1978**, *43*, 898.

(4) Kuivila, H. G.; Smith, G. F. *J. Org. Chem.* **1980**, *45*, 2918.

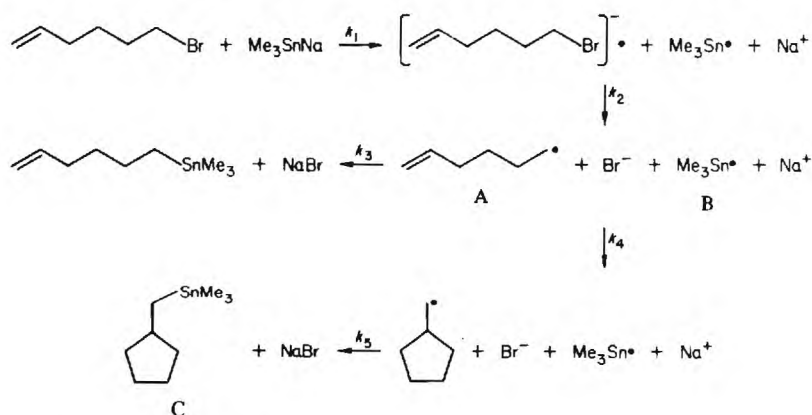
(5) Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833 and references therein.

(6) San Filippo, J., Jr.; Silberman, J. *J. Am. Chem. Soc.* **1981**, *103*, 5588. San Filippo, J., Jr.; Romano, L. *J. Org. Chem.* **1975**, *40*, 1514.

(7) Newcomb, M.; Courtney, A. R. *J. Org. Chem.* **1980**, *45*, 1707.

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

Scheme 1

Table I. Reactions of Cyclizable Probes with Me_3SnNa^a

expt no.	X in (probe)	order of addn ^b	additive, mol equiv	product yields, % ^c			
1	OTs	inv ^d	none	96	0.0	0.0	0.0
2	OTs	inv	10 DCPH	90	0.0	tr ^e	tr
3	Cl	inv	none	53	33 (0.65)	1.0	2.1 (1.6)
4	Cl	inv	10 DCPH	54	3.4 (0.57)	10.2	3.1 (1.8)
5	Br	nor	none	4.2	71 (0.27)	2.1	3.6 (1.6)
6	Br	inv	none	11	72 (0.31)	3.0	2.0 (1.3)
7	Br	inv	10 DCPH	1.0	14 (0.27)	49	16 (1.1)

^a Reactions were conducted at 0 °C in THF with reaction times of 3 h for chlorides and tosylates and 30 min for bromides and with equimolar amounts of reactants at 0.2 M initial concentration. Cyclizable probes^a and Me_3SnNa were prepared as previously described. ^b "Inverse" addition indicates that a solution of Me_3SnNa was added to the substrate, while "normal" indicates the substrate solution was added to the Me_3SnNa . ^c All new compounds were isolated by preparative GLC and gave satisfactory NMR, IR, and mass spectral and C-H analytical data. Yields were determined by GLC using internal standards. In experiments 1, 3, 5, and 6, dienes were formed (8% or less), presumably by dehydrohalogenation and disproportionation. In experiments 3 and 4, unreacted starting material accounts for the remainder of the material balance. ^d Inv = inverse; nor = normal. ^e Tr = trace.

Table II. Reactions of 2-Halo-octanes with Me_3SnNa^a

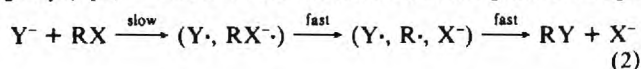
expt no.	X in R*-X	[α] ²⁵ _D ^{b,c} , deg	order of addn	concn of reactants, M	[α] ²⁵ _D for R*-SnMe ₃ products, deg		
					obsd	corr	ee, %
1	OTs	-7.55	inv ^d	0.2	+21.6	+28.4	100 ^e
2	OTs	-7.26	nor	0.2	+20.1	+27.5	96.8
3	Cl	+27.6	inv	0.2	-16.2	-21.9	77.1
4	Cl	+27.6	inv	0.4	-18.7	-25.3	89.0
5	Br	+31.0	nor	0.2	-10.1	-14.1	49.6
6	Br	+31.0	inv	0.2	-11.0	-15.4	54.2
7	Br	+31.0	inv	0.2	-10.6	-14.8	52.1
8	Br	+31.0	inv	0.4	-11.4	-16.0	56.3

^a For experimental conditions, see footnotes a-c of Table I. ^b Optical rotations were measured on a Jasco Model 5 ORD/CD instrument at λ 589 by using cyclopentane solutions. ^c The following maximum rotations ([α]²⁰_D) for the 2-halo-octanes were used: OTs, -9.93°; Cl, +37.3°; Br, +43.4°. ^d Inv = inverse; nor = normal. ^e The value of +28.4° was assumed to be the rotation of optically pure (+)-2-octyltrimethyltin.

amount of straight-chain hydrocarbon product (3–49%).

Since the results of the reaction of Me_3SnNa with the secondary bromide D indicate ET to be the major reaction pathway, the stereochemistry of the reaction of Me_3SnNa with a series of 2-halo-octanes was reexamined, with the results shown in Table II. The data show that the stereoselectivity of the reaction of 2-halo-octanes with Me_3SnNa decreases according to the trend OTs > Cl > Br. Although San Filippo reported that the stereochemistry of the reaction of Me_3SnNa with (-)-2-bromooctane depends on experimental parameters such as order of addition and concentration, we have found that such effects on product stereochemistry were marginal. Also the present work, utilizing cyclizable probes D, indicates complete inversion in a $\text{S}_\text{N}2$ fashion only for X = OTs, whereas San Filippo has indicated 98% inversion even for X = Br under some conditions.

In conclusion, the use of a cyclizable probe has provided additional evidence for the occurrence of radical character along the reaction pathway of the reaction of alkyl halides with Me_3SnNa . It is important to note that D (when X = Br) gave a 72% yield of cyclic substitution product on reaction with Me_3SnNa , indicating that at least 72% of the reaction proceeded via a process involving radical character along the reaction pathway while the reaction of Me_3SnNa with (+)-2-bromooctane proceeded with 77% inversion. We suggest that $\text{Me}_3\text{Sn}^\bullet$ (denoted by Y^\bullet) attacks the backside of the radical-anion pair ($\text{R}^\bullet, \text{X}^-$) in the solvent cage while the front side is still protected by the leaving group (eq 2).⁹ This is not unreasonable considering that the single



electron transfer between Y^- and RX should take place at the backside of the R group, and hence Y^- is still in close proximity to the backside of RX^- in the solvent cage when dissociation to R^\cdot and X^- takes place.¹⁰

Acknowledgment. We are indebted to the National Science Foundation, Grant No. CHE 78-00757, for support of this work.

Registry No. DCPH, 829-84-5; (trimethylstannyl)sodium, 16643-09-7; 6-bromo-1-heptene, 38334-98-4; 6-chloro-1-heptene, 15661-92-4; 6-(tosyloxy)-1-heptene, 59967-05-4; (-)-2-(tosyloxy)octane, 27770-99-6; (+)-2-chlorooctane, 16844-08-9; (+)-2-bromooctane, 1191-24-8; (\pm)-2-(trimethylstannyl)octane, 82949-86-8; (-)-2-(trimethylstannyl)octane, 79055-01-9; *cis*-2-methyl-1-(trimethylstannyl)cyclopentane, 80963-41-3; *trans*-2-methyl-1-(trimethylstannyl)cyclopentane, 80963-40-2; 1-heptane, 592-76-7; *cis*-1,2-dimethylcyclopentane, 1192-18-3; *trans*-1,2-dimethylcyclopentane, 822-50-4; 6-(trimethylstannyl)-1-heptene, 76879-52-2.

(9) After submission of this manuscript, a report appeared (Kitching, W.; Olsfowy, H. A.; Harvey, K. *J. Org. Chem.* **1982**, *47*, 1893) showing that 6-bromo-1-heptene gave substantial cyclic substitution product on reaction with Me_3SnLi , but the effect of leaving group and the relationship to the stereochemistry of the 2-octyl system were not examined.

(10) The scheme as presented in eq 2 implies that cyclization of the probe is competitive with the coupling step. Prior art would indicate that for coupling $k \sim 10^{10}$ and for cyclization $k = 10^5$. However, the data clearly show cyclization of the radical is competitive with coupling.

SUMMARY PROPOSAL BUDGET

ORGANIZATION Georgia Institute of Technology PRINCIPAL INVESTIGATOR/PROJECT DIRECTOR E. C. Ashby				FOR NSF USE ONLY			
				PROPOSAL NO.		DURATION (MONTHS)	
AWARD NO.				Proposed	Granted		
A. SENIOR PERSONNEL: PI/PD, Co-PI's, Faculty and Other Senior Associates (List each separately with title; A.6. show number in brackets)				NSF FUNDED PERSON-MOS.		FUNDS REQUESTED BY PROPOSER	FUNDS GRANTED BY NSF (IF DIFFERENT)
				CAL.	ACADSUMR		
1. E. C. Ashby					1.0	\$ 6,000	\$
2.							
3.							
4.							
5. () OTHERS (LIST INDIVIDUALLY ON BUDGET EXPLANATION PAGE)							
6. () TOTAL SENIOR PERSONNEL (1-5)							
B. OTHER PERSONNEL (SHOW NUMBERS IN BRACKETS)							
1. (1) POST DOCTORAL ASSOCIATES				12		17,000	
2. () OTHER PROFESSIONALS (TECHNICIAN, PROGRAMMER, ETC.)							
3. (3) GRADUATE STUDENTS						25,000	
4. () UNDERGRADUATE STUDENTS							
5. () SECRETARIAL-CLERICAL							
6. () OTHER							
TOTAL SALARIES AND WAGES (A+B)						48,000	
C. FRINGE BENEFITS (IF CHARGED AS DIRECT COSTS) 21% of A1						1,260	
TOTAL SALARIES, WAGES AND FRINGE BENEFITS (A+B+C)						49,260	
D. PERMANENT EQUIPMENT (LIST ITEM AND DOLLAR AMOUNT FOR EACH ITEM EXCEEDING \$1,000; ITEMS OVER \$10,000 REQUIRE CERTIFICATION)							
TOTAL PERMANENT EQUIPMENT							
E. TRAVEL 1. DOMESTIC (INCL. CANADA AND U.S. POSSESSIONS)						1,000	
2. FOREIGN							
F. PARTICIPANT SUPPORT COSTS							
1. STIPENDS \$							
2. TRAVEL							
3. SUBSISTENCE							
4. OTHER							
TOTAL PARTICIPANT COSTS							
G. OTHER DIRECT COSTS							
1. MATERIALS AND SUPPLIES						7,108	
2. PUBLICATION COSTS/PAGE CHARGES						1,000	
3. CONSULTANT SERVICES							
4. COMPUTER (ADPE) SERVICES							
5. SUBCONTRACTS							
6. OTHER							
TOTAL OTHER DIRECT COSTS						8,108	
H. TOTAL DIRECT COSTS (A THROUGH G)						58,368	
I. INDIRECT COSTS (SPECIFY)							
TOTAL INDIRECT COSTS 47.2% of Modified Total Direct Costs						27,550	
J. TOTAL DIRECT AND INDIRECT COSTS (H + I)						85,918	
K. RESIDUAL FUNDS (IF FOR FURTHER SUPPORT OF CURRENT PROJECTS GPM 252 AND 253)						-0-	
L. AMOUNT OF THIS REQUEST (J) OR (J MINUS K)						\$ 85,918	\$
PI/PD TYPED NAME & SIGNATURE E. C. Ashby <i>E.C. Ashby</i>				DATE 2/25/83	FOR NSF USE ONLY		
INST. REP. TYPED NAME & SIGNATURE Linda H. Bowman <i>Linda H. Bowman</i>				DATE 3/10/83	INDIRECT COST RATE VERIFICATION		
				Date Checked	Date of Rate Sheet	Initials - DGC	
						Program	

FINAL PROJECT REPORT

NSF FORM 98A

PLEASE READ INSTRUCTIONS ON REVERSE BEFORE COMPLETING

PART I-PROJECT IDENTIFICATION INFORMATION

1. Institution and Address Georgia Institute of Technology Atlanta, Georgia 30332	2. NSF Program	3. NSF Award Number
	4. Award Period From 6/1/81 To 11/31/84	5. Cumulative Award Amount \$51,500
6. Project Title Single Electron Transfer, A Major Reaction Pathway in Organic Chemistry		

PART II-SUMMARY OF COMPLETED PROJECT (FOR PUBLIC USE)

The work contained herein summarizes work accomplished during the past three years on the current NSF grant. Twenty-two publications have resulted showing that some of the most fundamental reactions in organic chemistry do not proceed by a polar pathway as originally thought, but rather by a single electron transfer (SET) pathway. Such reactions include the reaction of aromatic carbonyl compounds with Grignard Reagents, metal hydrides, alkoxides, dialkylamides, thioalkoxides, enolates and hydroxide ion as well as reactions of alkyl halides with most of the above nucleophiles. Name reactions such as Aldol Condensation, Claisen Condensation, Saponification and Cannizzaro reaction involving aromatic carbonyl compounds have also been shown to proceed by (SET). The present proposal suggests the completion of the scope of the above reactions, beginning work on several new reactions and, lastly, developing better methodology to investigate SET in systems in which it has been very difficult to detect.

PART III-TECHNICAL INFORMATION (FOR PROGRAM MANAGEMENT USES)

1. ITEM (Check appropriate blocks)	NONE	ATTACHED	PREVIOUSLY FURNISHED	TO BE FURNISHED SEPARATELY TO PROGRAM	
				Check (✓)	Approx. Date
a. Abstracts of Theses		X			
b. Publication Citations		X			
c. Data on Scientific Collaborators	X				
d. Information on Inventions	X				
e. Technical Description of Project and Results					
f. Other (specify)					
2. Principal Investigator/Project Director Name (Typed) E. C. Ashby	3. Principal Investigator/Project Director Signature E. C. Ashby <i>E.C. Ashby</i>			4. Date 7/3/85	

210. A.B. Goel, E.C. Ashby and R.C. Mehrotra, "Characterization of the Products of the Reaction of MgH_2 with Isopropylborate and Aluminum Isopropoxide in THF," Inorg. Chem. Acta., 62, 161 (1982).
211. E.C. Ashby, A. B. Goel and John N. Argyropoulos, "Evidence Supporting a Single Electron Transfer Pathway in the Reduction of Aromatic Ketones by Metal Alkoxides. Lithium Isopropoxide, an Excellent Reducing Agent for Aromatic Ketones", Tetrahedron Lett. 23, 2273 (1982).
212. E.C. Ashby, R. Scott Smith and A.B. Goel, "Comparative Studies on the Addition Reactions of the Normant Reagent (" CH_3MgBr " + $CuBr$) and the New Tetrahydrofuran - Soluble Magnesium Methyl Cuprates $Mg_mCu_n(CH_3)_{m+n}$ with Phylacetylene", J. Org. Chem., 46, 5133 (1982).
213. E.C. Ashby and Robert DePriest, "Evidence for Inversion of Configuration in Reactions Involving Radical Intermediates", J. Amer. Chem. Soc., 104, 6144 (1982).
214. E.C. Ashby, J.N. Argyropoulos, G. Richard Meyer and A.B. Goel, "Evidence for a Single Electron Transfer Mechanism in Aldol Condensation Reactions", J. Amer. Chem. Soc. 104 (6788), (1982).
215. E.C. Ashby, R.N. DePriest, A. Tuncay and Sushil Srivastava, "Evidence for a Single Electron Transfer Mechanism in Reactions of Lithium Diorganocuprates with Organic Halides", Tetrahedron Lett. (2351) (1982).
216. E.C. Ashby, "Single Electron Transfer in Organic Chemistry", McGraw-Hill Yearbook of Science and Technology, (1982).
217. E.C. Ashby and R.D. Ainslie, "Hydrometallation of 1-Octene with Grignard Reagents, Magnesium Alkyls and Alkylmagnesium Hydrides Catalyzed by Bis-(Cyclopentadiene) Titanium Dichloride", J. Organometall Chem., 250 1 (1983).
218. E.C. Ashby and A.B. Goel, "The Solution Composition of the Normant Reagents. Identification of New THF Soluble Magnesium Methylcuprates, $Cu_nMg_mMe_{2m+n}$ ", J. Org. Chem., 48, 2125 (1983).
219. E.C. Ashby, David Coleman, III and M. Pillar Gramasa, "Evidence Supporting a Single Electron Transfer Pathway in the Cannizzaro Reaction", Tetrahedron Lett., 24, 851 (1983).
220. E.C. Ashby and Won-Suh Park, "Evidence for Single Electron Transfer in Claisen Condensation. The Reaction of Ethyl p-nitrobenzoate with the Lithium Enolate of Pinacolone", Tetrahedron Letter., 24, 1667 (1983).
221. A.B. Goel and E.C. Ashby, "The Reaction between Dimethylmagnesium and Lithium Aluminum Hydride in Diethyl Ether and Tetrahydrofuran," Inorg. Chim. Acta., 87, 61 (1984)
222. E.C. Ashby, Bernd Wenderoth, Tung N. Pham and Won Suh Park, "Evidence for Single Electron Transfer in the Reduction of Organic Halides by Lithium Triethylborohydride," J. Org. Chem., 49, 4505 (1984).

223. E.C. Ashby, R.M. DePriest and Wei-Yang Su, "Electron Transfer in the Reactions of Alkyl Halides with Sodium Trimethyltin," Organometallics, 3, 1718 (1984).
224. E.C. Ashby, Dong-Hak Bae, Won-Suh Park, Robert N. DePriest and Wei-Yang Su, "Evidence for Single Electron Transfer in the Reaction of Alkoxides with Alkyl Halides," Tetrahedron Lett. 25, 5107 (1984).
225. E.C. Ashby, R.N. DePriest, and T.N. Pham, "Concerning the Reduction of Alkyl Halides by LiAlH_4 . Evidence that AlH_3 Produced In Situ is the One Electron Transfer Agent," Tetrahedron Lett. 2825 (1984).
226. E.C. Ashby and T.N. Pham, "(Endo-5-(2-Haloethyl)-2-Norbornene. A New Radical Probe," Tetrahedron Lett., 25, 4333 (1984).
227. E.C. Ashby, R.N. DePriest, A.B. Goel, Bernd Wenderoth and Tung Pham, "Occurrence of Electron Transfer in the Reduction of Organic Halides by LiAlH_4 and AlH_3 , J. Org. Chem., 49, 3545 (1984).
228. E.C. Ashby and J.N. Argyropoulos, "Evidence for Single Electron Transfer in the Reaction of a Lithium Enolate with a Primary Alkyl Iodide," Tetrahedron Lett., 25, 7 (1984).

SINGLE ELECTRON TRANSFER IN REACTIONS
INVOLVING ALKYL HALIDES AND ESTERS WITH NUCLEOPHILES

A THESIS

Presented to

The Faculty of the Division of Graduate Studies

By

Won-Suh Park

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy in the School of Chemistry

Georgia Institute of Technology

March 1984

SUMMARY

A variety of organic substrates possessing low reduction potentials and producing stable radical intermediates by one electron reduction have been utilized in order to evaluate the one electron transfer abilities of lithium thiolates. Thus, direct spectroscopic detection of radical intermediates was made for reactions of lithium thiolates with diaryl ketones, polynuclear hydrocarbons, trityl halides and 9-bromofluorene.

A mechanistic study for the reaction of lithium thiolates with trityl halides was conducted in more detail by (1) carrying out a complete identification of products, (2) studying the effect of the radical trap, DCPH, on product distribution, and (3) studying the effects of light and the presence of p-DNB on the reaction rate. Thus, reactions of lithium alkanethiolates with trityl halides produced α -substitution product (Ph_3CSR), and p-substitution product ($\text{p-RSC}_6\text{H}_4\text{CHPh}_2$), as well as radical by-products such as reduction product (Ph_3CH), dimerization product of trityl radicals ($\text{p-Ph}_3\text{CC}_6\text{H}_4\text{CHPh}_2$), and dimerization product of thiyl radicals (RSSR), which suggests the occurrence of SET as a predominant pathway. The presence of DCPH in the reaction of alkanethiolate with trityl halide diverted the α -substitution product as well as radical by-products to formation of the reduction product (Ph_3CH), suggesting α -substitution product as a result of non-geminate coupling of trityl and thiyl radicals. Carrying out the reaction of lithium 2-propanethiolate with trityl bromide in THF in the presence of light or absence of light or the presence of p-DNB did not affect the rate of reaction thus suggesting

the unlikelihood of a radical-radical anion chain process.

Studies of the reaction of lithium thiolates with the cyclizable alkyl iodide probe, 2,2-dimethyl-1-iodo-5-hexene yielded straight chain substitution products quantitatively. However the same reactions in the présence of the radical trap, DCPH, yielded up to 30% hydrocarbon products, suggesting a significant contribution of radicals and hence a SET pathway to describe this nucleophilic substitution reaction. For the reaction of lithium thiolates with cyclizable alkyl bromide and tosylate probes, no evidence supporting SET pathway was observed.

In the Claisen Condensation, reaction of the lithium enolate of pinacolone with ethyl p-nitrobenzoate, a paramagnetic intermediate was detected by epr spectroscopy. The concentration of a paramagnetic radical species generated in the reaction was shown to decrease in a first order fashion with a similar rate constant compared to the first order rate constant describing the rate of formation of condensation product. It was also found that the rate of disappearance of the reactant, ethyl p-nitrobenzoate, was similar to the rate of appearance of the paramagnetic intermediate under the pseudo-first order conditions.

Thus, it has been demonstrated that the reaction of p-nitrobenzoate esters with the lithium enolate of pinacolone takes place mainly via a SET pathway. However, attempts to detect the involvement of SET in reactions involving other aromatic esters using the same methods as above were largely unsuccessful.

The paramagnetic intermediate in the Saponification reaction of ethyl p-nitrobenzoate with NaOH in anhydrous solvent systems, such as THF-HMPA (9:1) and EtOH-HMPA (1:4), was detected by epr spectroscopy.

In the reaction carried out in EtOH-HMPA (1:4) homogeneously, the concentration of the paramagnetic intermediate was shown to decrease in a first order fashion with a similar rate constant to the first order rate constant of the formation of the saponification product. Thus, it has been demonstrated that the saponification reaction of ethyl p-nitrobenzoate by NaOH in EtOH-HMPA (1:4) takes place mainly via a SET pathway. An attempt to detect the paramagnetic intermediate in the reactions of methyl p-trifluoromethyl benzoate and methyl p-chlorobenzoate with NaOH was not successful.

ORGANIC REACTIONS INVOLVING ELECTRON TRANSFER

A THESIS

Presented to

The Faculty of the Division of Graduate Studies

By

Robert N. DePriest

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy in the School of Chemistry

Georgia Institute of Technology

August 1982

SUMMARY

A series of experiments designed to demonstrate the occurrence of radical intermediates in an electron transfer pathway for a variety of reactions have been conducted. The experimental methods employed include product studies of reactions of compounds containing structures which can undergo a characteristic radical rearrangement (such as the conversion of 5-hexen-1-yl to cyclopentylmethyl radical), stereochemical studies, direct observation of stable radical intermediates by electron paramagnetic resonance studies and radical trapping experiments.

The cleavage of Grignard reagents designed to demonstrate the occurrence of electron transfer via a radical rearrangement has been examined with two types of electrophiles, biaryl ketones and molecular halogens. In the former case, the diagnostic cyclization was observed, which is an indication that electron transfer is a feature of the reaction pathway in the addition of Grignard reagents to biaryl ketones. In the latter case, no diagnostic rearrangements were observed, which indicates that no radical species are formed on the reaction pathway which have lifetimes sufficient for rearrangements to occur.

A variety of methods have been utilized in order to evaluate the occurrence of an electron transfer pathway for the reduction of organic halides by main-group metal hydrides. Thus, direct spectroscopic observation of a radical intermediate was made in the reduction of trityl bromide by LiAlH_4 . The reductions of a series of alkyl halides containing cyclizable radical probes were also examined and electron transfer was

found to be the predominant pathway for reactions of various hydride reagents with 6-iodo-1-heptene and with 2,2-dimethyl-1-iodo-5-hexene, since cyclized hydrocarbons were major products in these reactions. Additional evidence indicative of radical intermediates in these reductions were obtained from reactions of the iodo compounds with LiAlD_4 in the presence of the radical trap DCPH, which was shown to transfer a hydrogen atom to the radical intermediates. However, the cyclizable alkyl halide probes in which the leaving group is tosylate, chloride or bromide were reduced by metal hydrides to produce only straight-chain hydrocarbons, with the exception of 1-bromo-2,2-dimethyl-5-hexene which gave equal amounts of cyclic and straight-chain reduction products upon reaction with LiAlH_4 . Thus, the studies of the reductions of the cyclizable alkyl halide probe compounds indicate that the electron transfer pathway is much more favorable for iodo compounds as compared to compounds with other leaving groups.

The stereochemistry of the reduction of organic halides by LiAlD_4 in THF was also examined. It has been shown that (-)-1-chloro-1-phenylethane and (-)-1-bromo-1-phenylethane are reduced by LiAlD_4 with predominant inversion of configuration. Also, (-)-2-tosyloctane, (+)-2-chlorooctane and (+)-2-bromooctane are reduced by LiAlD_4 with the same stereospecificity, but (+)-2-iodooctane is reduced by LiAlD_4 with substantially less stereospecificity. Thus, these stereochemical studies also indicate that an electron transfer pathway is operative for the reduction of secondary alkyl iodides by LiAlD_4 .

The studies of the reactions of cyclizable secondary alkyl halides (6-halo-1-heptenes) with sodium trimethyltin have demonstrated the

occurrence of an electron transfer pathway, since tetraalkyltin products containing a cyclized alkyl group were formed. The extent of electron transfer was found to be a function of the leaving group and follows the trend $I=Br>Cl$ and no electron transfer was observed for the OTs leaving group. The radical trapping agent DCPH was found to be very effective in trapping the radical intermediate to form the hydrocarbon product instead of the tetraalkyltin product. Also, it was shown that the reaction of sodium trimethyltin with the 2-halo-octanes proceeds with predominant inversion of configuration. Thus, it has been shown that the reaction of sodium trimethyltin with secondary alkyl halides proceeds by an electron transfer pathway to form an intermediate with sufficient radical character to undergo cyclization or be trapped by DCPH, but also the intermediate is converted to tetraalkyltin product with predominant inversion of configuration.

By examining the products of reactions of cyclizable alkyl halides with various nucleophiles the possible occurrence of electron transfer pathways has been evaluated. Thus, it was shown that alkali metal alkoxides, thioalkoxides and enolates do not act as electron transfer agents toward alkyl halides, since no cyclized products were observed in these systems. However, it has been demonstrated that radical intermediates are formed in reactions of lithium alkylamides and lithium alkylcuprates with iodo compounds, since large amounts of cyclized products were formed from the cyclizable probes in these reactions.